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|---|---|
| Item Type | Book |
| Authors | Nuffield Council on Bioethics |
| Publisher | Nuffield Council on Bioethics |
| Rights | With permission of the license/copyright holder |
| Download date | 2026-09-14 11:31:27 |
| Link to Item | http://hdl.handle.net/20.500.12424/184928 |

# The ethics of research involving animals

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**Published by**
**Nuffield Council on Bioethics**
**28 Bedford Square**
**London WC1B 3JS**

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**ISBN 1 904384 10 2**
**May 2005**

**To order a printed copy please contact the Nuffield Council or visit the website.**

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Designed by **dsprint / redesign**
7 Jute Lane
Brimsdown
Enfield EN3 7JL

Printed by **Latimer Trend & Company Ltd**
Estover Road
Plymouth PL6 7PY

# The ethics of research involving animals

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1 to identify and define ethical questions raised by recent advances in biological and medical research in order to respond to, and to anticipate, public concern;

2 to make arrangements for examining and reporting on such questions with a view to promoting public understanding and discussion; this may lead, where needed, to the formulation of new guidelines by the appropriate regulatory or other body;

3 in the light of the outcome of its work, to publish reports; and to make representations, as the Council may judge appropriate.

**The Nuffield Council on Bioethics is funded jointly by
the Medical Research Council, the Nuffield Foundation and the Wellcome Trust**

# Foreword

The issues addressed in this Report have been a subject of intense public debate over at least the past four hundred years. Feelings are strong on all sides of the issues, and in recent years reports of violent action against those conducting animal research in the UK have brought the matter to the forefront of public attention.

Members of the Working Party, like members of the public, hold many different and sometimes opposing views. Nevertheless, the group has been able to conduct its inquiry in an atmosphere conducive to gaining a better understanding of the scientific and ethical issues involved, and avoiding the polarisation of views which has so often stifled proper debate. It is in this spirit that we present our Report.

Throughout the Working Party's meetings, many varied opinions were quite properly represented and argued through, and we have tried to analyse the ethical bases on which different opinions are held. A respect for the basis of beliefs different from one's own has enabled members of the group to agree on a consensus statement and to present conclusions and recommendations which, while not always necessarily representing the views of all, do as comprehensively as possible offer a clarification of the debate. Where widely different views are held, we have sought to set them out as clearly as possible. This approach, we believe, should contribute to fair and balanced discussions among individuals and to decision making by those in government or other official and regulatory bodies.

We have been conscious that conclusions about the use of animals involved in research, diverse as this is, must be seen in the wider context of the use of animals in food, in clothing, as pets and as working animals in farming and other occupations. Science, however, is progressing rapidly in new technologies such as cloning, genetic modification and also in the development of alternatives to the use of animals. The Report sets out in some detail the range of scientific uses of animals including the uses being made of these new advances. It considers the ethical issues of research involving animals in the light of these developments, the implications for regulation, and the provision of information and education.

As Chair of the Working Group, I would like to record my thanks to all members, who have worked so hard to produce a Report which, I hope, will genuinely provide helpful analysis and insight into this topic, often at great personal cost. I also thank the Council for their help and advice throughout the two years of the Group's work. We all owe a great debt also to the Secretariat who have taken the burden of producing a long and comprehensive Report, agreed as fair and balanced by the Group as well as by those who so helpfully read and refereed early drafts for us. I should like to pay special tribute to Harald Schmidt, Secretary to the Working Party, whose skills and knowledge were invaluable.

We hope that the Report will be a useful starting point of reference for all those concerned with this important issue in the time ahead.

**Baroness Perry of Southwark**

# Acknowledgements

The Council wishes to thank the members of the Working Party for their contribution. Their expertise has been invaluable. It also wishes to thank the many organisations and individuals who have responded to the invitation to comment on the Consultation paper. The Council is very grateful to Professor Nancy Rothwell, Professor Sir Patrick Bateson, Professor Mary Midgley, Professor Stephen Clark, Professor Alan Holland, Dr Ray Hill, Dr Gill Langley, Dr Richard Ryder, Mike Radford and David Thomas who reviewed an earlier version of this Report. Their comments were extremely helpful. It further wishes to thank the following individuals who provided valuable insights in fact-finding meetings: Michele Corrado, Dr Gill Samuels, Graham Moore and colleagues, Rosie Barnes, Christine Cryne, Robert Meadowcroft, Dr Patricia Coulson, Dr Betsy Pownall, Dr Harv Isaacs, Professor Henry Leese, Professor Alan Wilson, Mike Snelling, Professor Alistair Fitter, Piran White, Professor Geoff Hall, Dr Chris Springall and colleagues, Professor Michael Balls, Dr Gill Langley, Dr Jon Richmond, Professor Michael Banner, Richard West, Dr Ray Greek, Kathy Archibald, Professor Roger Lemon, Robert Walker, Martin Lawton, John Frogley, Brian Cass, Andrew Gay, and David Whittaker. The Council and the Working Group are also grateful to individuals who responded to requests for advice on specific parts of the Report, including Professor Colin Allen, Professor Marc Bekoff, Dr Derek Fry, Dr Penny Hawkins, Dr Gill Langley, Professor David Morton, Dr Barry Philips, Dr Jon Richmond, Dr Vicky Robinson, Stefan Schleim, Dr Jane Smith, Dr Peter Thornton, Martin Walsh, and David Wood.

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# Terms of reference

1 To review recent, current and prospective developments in the scientific use of non-human animals, including genetic modification or cloning;

2 To assess the ethical implications of these developments, and, in doing so, to consider arguments about the differing status of various non-human animals and the implications of such arguments on their use in research;

3 To examine ways of assessing the costs and benefits of the scientific use of non-human animals;

4 To assess ways of regulating and enhancing good practice;

5 To assess the ethical implications of using alternatives to non-human animals in different fields of research;

6 To identify and review developments and differences internationally in the use of non-human animals in research and its regulation;

7 To explore ways of stimulating public debate and providing information and education about the issues involved.

# Summary and recommendations

## I. Background and introduction

Issues raised by research[1] involving animals have aroused intense debate, particularly in the UK. Opinion about its necessity, justification and acceptability varies widely. Discussion on the subject is often portrayed as being essentially between two positions that are either 'for' or 'against' the use of animals. This is unhelpful, since the matter itself is complex, as are the many views that surround it. A very brief overview would need to include at least the following range of positions.

One group favours the use of animals in research and emphasises the scientific and medical benefits that have arisen. Supporters of this view include most medical-research charities, many patient groups, the current UK Government and most members of the scientific community using animals. They point out that the use of animals in research has made a substantial contribution to our understanding of biological processes, and that it has been responsible for many important biomedical discoveries, including the development of a great number of therapies and preventative treatments, such as antibiotics, insulin, vaccines and organ transplantation. The development of most modern medicines has also involved animals in research and testing. Proponents, noting that in the UK animal research is strictly regulated, argue on both ethical and scientific grounds, that it must continue to alleviate suffering and to advance scientific knowledge.

Others also draw on ethical and scientific arguments but come to a different conclusion, arguing for an end to animal research. Some take absolutist positions. For example, a few campaigning organisations question the scientific validity of all animal research and want an immediate end to the practice because they believe that results from biomedical experiments on animals are not transferable to humans. Others are less focused on the scientific issues, and more concerned with the fundamental ethical question of whether it is right for humans to subject sentient animals to procedures that may cause them pain and suffering, and from which they will not benefit. Emphasising that animals cannot consent to such procedures they take an absolutist ethical position, arguing for an end to all harmful research, regardless of the consequences for human, scientific and medical progress.

A range of further positions can be found in the debate, as many people may have sympathy for some assumptions, but reject others made by those taking the two positions described above. For example, not all animal research is undertaken to advance medical progress, and some people question whether all uses are equally necessary and justifiable. They may therefore have concerns, for example, about basic research, where the usefulness of the knowledge produced may not always be clear, or certain forms of toxicity testing, where animals may experience considerable suffering. Others argue that research involving animals is too often perceived as the only means of addressing specific research questions, or that insufficient effort is made in exhausting the potential of scientific methods that do not use animals.

In 2003, the Nuffield Council established a Working Party to examine the debate in more detail, and to clarify the complex ethical issues raised by research involving animals. In this Summary of the Report we present:

- a brief outline of the focus and structure of the Report;
- a consensus statement, which summarises the agreement of all members of the Working Party on a number of general issues (Box 1);
- our principal observations with regard to the scientific rationale for using animals in different

[1] In this Report, we generally use the term 'research' in a broad sense, encompassing experiments undertaken in basic and applied research, as well as for the purpose of toxicity testing. We use the term 'testing' to refer exclusively to toxicity testing.

kinds of research and testing;

- an overview of the way in which ethical issues have been considered; and
- recommendations and conclusions arising from the consensus statement, and the discussion of scientific and ethical issues.

## II. The structure and focus of the Report

The focus of this Report is on ethical issues raised by research involving animals. After a more detailed introduction (Chapter 1) and a description of the past and present context of the debate (Chapter 2), we present an outline of the ethical issues in Chapter 3. This chapter does not seek to explain or defend individual or collective positions of members of the Working Party but rather aims to provide the reader with an overview of the kind of questions that are posed by animal research. Since the degree to which animals involved in research experience pain, suffering and distress is central to the debate, we explore philosophical and practical aspects of assessing these states in animals (Chapter 4). Having provided this background we then describe a range of different scientific uses of animals which includes basic research to understand how animals develop and function (Chapter 5), the use of animals for the study of human disease (Chapter 6), genetic modification of animals in the study of disease (Chapter 7), the development of medicines and vaccines by the pharmaceutical industry (Chapter 8) and toxicological testing of potentially hazardous compounds for animals, humans or the environment (Chapter 9). We consider the scope and potential of methods that seek to replace, reduce or refine animal research In Chapters 11 and 12. After an outline of the regulatory context (Chapter 13) we resume the ethical discussion in Chapter 14 and present the views of the Working Party, inviting readers to compare their own judgements in the light of the Report with that of the Working Party. Our recommendations are presented in Chapter 15.

### Box 1: Consensus statement by all members of the Working Party (paragraphs 15.3–15.20)

***Research involving animals and other uses of animals***

It is important to consider the ethical issues raised by animal experimentation in the wider context of the other uses of animals in society, and to take into account:

- the impact on the lives and welfare of animals that different uses have;
- the broader consequences if there were a ban on using animals in specific circumstances;
- a comparison of the benefits arising from the different uses of animals; and
- the numbers of animals involved.

The involvement of animals in research cannot be justified simply by the fact that animals are used or abused in other ways. Each use requires special consideration. Members of the Working Party noted during their own discussions and in considering responses to the Consultation that views on animal research were not always consistent with views on other uses of animals. Awareness that contradictory views are often held simultaneously is an important first step in considering the ethical issues raised by animal research.

***The benefits of research involving animals***

Historically, animals have been used in a wide range of scientific research activities that have provided many benefits to society, particularly in relation to the advancement of scientific knowledge, human and veterinary medicine, and the safety of chemical products.

Some of these advances might have been achieved by other means, although we cannot know this. Neither can we know what a world would look like in which animal research had never been undertaken. Hypothetically, there may have been other options which could have produced acceptable levels of knowledge and healthcare. These levels might have been lower than our current standards, but perhaps if society had deemed the use of animals for research as unacceptable, there would have been acceptance of greater limitations on scientific and medical progress. Alternatively, it is conceivable that equally good or better progress might have been achieved with other methods. The Working Party agrees that speculation about whether or not acceptable standards in basic and applied research could have been achieved in the past by means other than the use of animals is less important than the question of assessing the consequences of continuing or abandoning animal experimentation now.

It is sometimes assumed that to end animal research would be to end scientific and medical progress, but such generalisation is unhelpful. The UK Government has responded to changes in the moral climate by introducing policies that have ended some types of animal research and testing in the UK. For example, the use of animals for the testing

*Continued*

of cosmetic products and their ingredients, alcohol and tobacco has ceased. Similar policies are in place regarding the use of the great apes. Independent of the moral acceptability of research, the scientific costs and benefits of abandoning specific types of animal research need to be assessed on a case by case basis. On the one hand, the possibility of the emergence of new diseases may require a reassessment of whether the abandonment of specific types of research is still justified. On the other, scientific advances that could replace the use of animals in some areas may enjoin us to assess whether further policies should be introduced to terminate these uses of animals accordingly.

The validity, usefulness and relevance of specific types of animal research, for example in relation to the use of animals for the study of human diseases, needs to be ascertained in each individual case.

***Desirability of a world without animal research***

All research licensed in the UK under the Animal (Scientific Procedures) Act 1986 (A(SP)A) has the potential to cause pain, suffering, distress or lasting harm to the animals used. Most animals are killed at the end of experiments. A world in which the important benefits of such research could be achieved without causing pain, suffering, distress, lasting harm or death to animals involved in research must be the ultimate goal.

We have considered the different arguments advanced in favour and against continuing specific types of animal research in Chapters 3 and 14. Some believe the imperative to protect animal welfare should be overriding, whereas others believe that the moral arguments favour the continuation of research on animals. All members of the Working Party acknowledged that these viewpoints arise from moral convictions that should be given serious consideration. This approach requires open-mindedness in trying to understand the reasons and arguments of others. Genuine willingness is also required to test and, where necessary, revise one's own moral framework.

While we trust that more progress in the moral debate can be made, we are aware that, for the near future, further moral argument alone cannot provide a universal answer as to whether or not research on animals is justified. But practical advances in scientific methods can reduce areas of conflict. For this reason, the importance of the Three Rs (Refinement, Reduction and Replacement), and especially of the need to find Replacements, cannot be overstated.

***The ethical importance of the Three Rs***

The Working Party therefore concludes that it is crucial that the Three Rs are, and continue to be, enshrined in UK regulation on research involving animals. The principle that animals may only be used for research if there is no other way of obtaining the results anticipated from an experiment is also fundamental. Furthermore, we observe that for moral justification of animal research it is insufficient to consider only those alternatives which are practicably available at the time of assessing a licence application. The question of why alternatives are not available and what is required to make them available must also be asked. The potential of the Three Rs is far from being exhausted. The Working Party therefore agrees that there is a moral imperative to develop as a priority scientifically rigorous and validated alternative methods for those areas in which Replacements do not currently exist. It is equally important to devise mechanisms that help in the practical implementation of available validated methods.

In applying the Three Rs it is crucial to consider not only the context of the experiments themselves but also the many other factors that can affect animal welfare, including breeding, transportation, feeding, housing, and handling. The quality of these factors and especially the ability of animals to satisfy their species-specific needs can usually be improved.

***Regulation***

We acknowledge that the UK has the most detailed legislative framework concerning research on animals in the world. But proper attention to the welfare of animals involved in research and the accountability of scientists who conduct research on animals cannot be achieved merely by having detailed regulations. Regulation can act as an emotional screen between the researcher and an animal, possibly encouraging researchers to believe that simply to conform to regulations is to act in a moral way. It is therefore crucial to promote best practice more actively and to improve the culture of care in establishments licensed to conduct experiments on animals.

When considering the replacement of specific types of research by alternative methods, it is important to take account of the international context in which research involving animals takes place. Many chemical and pharmaceutical compounds that have been developed are being marketed in countries or regions that have different regulatory frameworks for animal research and testing. There is a range of alternatives that have been internationally accepted for safety testing. Nonetheless, many Replacements are not universally accepted, and the process of validation is lengthy. These processes need to be optimised and initiatives aimed at abandoning and replacing specific types of animal testing at national levels complemented by initiatives at the international level. This is not to say that initiatives in the UK can only be taken once there is consensus at an international level. In the past, the UK has been a leader in working towards change in international policies related to research involving animals. This leadership should be encouraged.

***Duplication of experiments on animals***

Scientific experiments involving animals are sometimes repeated by the same or other research groups. In considering whether the repetition of such experiments should take place, it is important to distinguish between *duplication* and *replication* of experiments:*

- Duplication of harmful animal experiments is in principle unacceptable. We use the term to describe cases where there is insufficient scientific justification for the repetition. It occurs primarily when the scientist either does not know that another has carried out the experiment or test in question, or when he does know, but is unable to attain reasonable access to the information.
- Replication refers to repetition of experiments or tests where this is necessary for sound progress in scientific

*Continued*

enquiries. The scientific method demands that research findings need to be corroborated by the same and other research groups, in order to establish the validity of the results.

The Working Party acknowledges that academic competitiveness and commercial confidentiality can sometimes complicate the sharing of information. But at its best, science is an open process, and mechanisms that prevent the sharing of information need to be reviewed carefully in terms of their justification and implications for the use of animals in research.

***The context of the debate***

The majority of researchers who use animals consider that despite progress in the implementation of the Three Rs, animal research will remain an essential part of their work. Furthermore, certain provisions in the current regulatory framework for approval of chemical products and medicines require tests involving animals. We conclude that it is unrealistic to assume that all animal experimentation will end in the short term. It is crucial, therefore, to create a climate in which the necessity and justification for using animals is assessed and discussed fairly and with due respect for all views.

Constructive debate would be facilitated by the provision of clear information about the full implications of research involving animals in terms of the kind, numbers and species of animals used, as well as the pain, suffering and distress to which they can be subjected. It is equally important that society should be informed about the scientific, medical and other benefits of research involving animals. Information about selected aspects of research without provision of any further context can be misleading.

All members of the Working Party agree that the use of violence and intimidation against members of the research community, research institutions, their business partners, family and neighbours, or against organisations and people representing animal welfare groups, is morally wrong and politically insidious. The freedom to promote or oppose research involving animals peacefully and democratically, however, must be maintained.

* Sometimes, animals are used in repeated experiments for the purpose of education or training. However, we have not addressed the issues raised by this particular use here, see paragraph 1.18.

## III. The scientific rationale for using animals in research and testing

Although the focus of this Report is on the ethical issues raised by animal research, we also need to consider scientific questions. For if it were the case that harmful animal research provided no useful knowledge or application, it would be difficult to see how it could be morally justified. Similarly, it is important to assess which potential scientific benefits might have to be forgone, if animal research or testing in general, or in particular areas, were to be reduced or abandoned, and could not be replaced adequately by scientific methods that do not involve animals. The two principal questions which this Report seeks to clarify are therefore:

- does the scientific use of animals lead to valid, useful and relevant results in specific areas?
- is it permissible for one species to cause pain, suffering and death to another to achieve aims that benefit primarily the former species?

Across and within each area of research involving animals described in Chapters 5–9 the intended and realised benefits take a wide range of forms. Three main types can be distinguished.

- *Advancing scientific knowledge*

  Some research, predominantly basic research, has no direct application and its primary purpose is to advance scientific knowledge about the way animals behave, or develop and function biologically. The study of basic physiological processes and genetic mechanisms also falls into this category (Chapter 5).

- *Using animals as models for humans to study disease mechanisms and develop interventions*

  Animals are used as models for humans to understand disease processes and to develop effective preventative and therapeutic measures such as vaccines or medicines (Chapters 6–8). Some of these interventions may also be used in, or have been developed specifically for, animals. Such research often draws on findings from basic research.

- *Animals as models in toxicity testing*

  Animals are used to test the safety of a range of compounds that are potentially hazardous for animals, humans or the environment (Chapter 9).

We begin our discussion with the assumption that whether or not research in these areas yields valid, useful and relevant results needs to be judged on a case by case basis. For practically all basic research it can be argued that data produced are valid insofar as it is conducted in a methodologically sound manner, since any such completed research project adds to the scientific body of knowledge (provided results are made reasonably available to the scientific community). The controversies about the acceptability of basic research therefore focus primarily on its usefulness and relevance, and on the ethical question of whether it is necessary and justifiable, if it causes specific degrees of pain, suffering or distress to the animals involved (paragraphs 3.53 and 14.38). The question of validity, usefulness and relevance is more complicated when animals are used as models for humans, as the question of whether reliable extrapolations can actually be made from one species to the other, needs to be addressed. Accordingly, we consider:

- the biological basis for using animals as models for human diseases (paragraphs 4.8–4.10);
- examples of research where it has been possible to make valid and useful inferences (see for example, Box 5.2, paragraphs 6.4–6.31, 7.7–7.8, Boxes 8.1, 8.2 and 8.3, paragraphs 9.5–9.7);
- examples of research where progress has been difficult (paragraphs 6.33–6.39);
- claims that the very concept of using animals as models for humans is flawed, misleading and dangerous because a small number of products such as medicines that have involved animal research and testing in their development were withdrawn from the market because of adverse reactions in people (Boxes 8.6 and 8.7).

***Conclusion on the scientific validity of animal research and testing***

We conclude that because of evolutionary continuities in the form of behavioural, anatomical, physiological, neurological, biochemical and pharmacological similarities between animals and humans there are sufficient grounds for the scientific hypothesis that, in specific cases, animals can be useful models to study particular aspects of biological processes in humans, and to examine the effects of therapeutic and other interventions.

In view of the examples of research considered in Chapters 5-9 we refute two commonly encountered generalisations about research involving animals that is undertaken with the aim of yielding results that are applicable to humans: (i) that all such research is directly applicable to humans or (ii) that no animal research has ever produced results that are useful and relevant to humans. Each type of research or testing has to be judged on its own merits (paragraph 10.46). We therefore agree with the conclusion made in a recent Report by the Animal Procedures Committee (APC) that the scientific validity of animal experiments is:

> 'a condition capable of being fulfilled, but has to be judged case by case and subjected to detailed critical evaluation.'[2]

## IV. Ethical issues raised by animal research

We begin the exploration of ethical issues raised by animal research in Chapter 3 by considering five main types of ethical question (Box 2). For each question, we consider commonly encountered arguments to bring clarity to the debate, to identify agreement where it exists, and to understand the rationale for the remaining disagreement.

***The question of moral status***

The debate about research involving animals is often reduced to the question of defining the moral status (or moral importance) of humans, and animals. We identify three views (paragraph 3.20).

2 Animal Procedures Committee (2003) *Review of the cost-benefit assessment in the use of animals in research*, p26, available at: http://www.apc.gov.uk/reference/costbenefit.pdf. Accessed on: 4 April 2005.

- There is something special about humans, and all humans possess some morally vital property that all animals lack (the *clear-line view*).
- There is a hierarchy of moral importance with humans at the apex, followed by primates and then other mammalian species such as pigs, dogs, rats and mice and other vertebrates such as zebrafish, with invertebrates (for example fruit flies) and single-celled creatures arranged towards the bottom (the *moral sliding scale view*).
- There is no categorical distinction between human and non-human animals, and that they are moral equals (the *moral equality view*).

**Box 2: Ethical questions raised by animal research**

- Provided there are substantial benefits associated with research involving animals, why should the use of animals require special justification?
- Can any use of animals by humans be justified? Which specific issues need to be considered in the context of research?
- What role does the unavailability of alternatives play in the justification of research involving animals?
- How does the justification of animal research relate to the justification of other uses, such as food production?
- What is the appropriate role of regulation for research involving animals?

We conclude that neither consideration of the relative moral status nor reference to the evolutionary order or uses of animals in other contexts (paragraphs 3.21-3.26), settles the question of the permissibility of animal experimentation, or of any other use of animals in a helpful manner. Exclusive focus on the concept of moral status may obscure more than it illuminates (paragraph 3.24).

***Morally relevant features***

We suggest instead that a promising approach is to ask what *features* of humans and animals can qualify them as moral subjects, imposing constraints or limits on how they may be treated. We do not start from the assumption that there is one 'master property' or overriding criterion. Nor, for the purpose of the discussion in Chapter 3, do we assume that there are some species that should never be used for any purpose, or that the acceptability of using species depends on how closely related they are to humans in evolutionary terms. We explore the possibility that there are no less than the following five morally relevant features. At least one, or all of these, may be applicable to specific animals, albeit to differing degrees, and with subtly distinct moral consequences:

- sentience (paragraphs 3.28–3.29);
- higher cognitive capacities (paragraphs 3.30–3.36);
- the capacity to flourish (paragraphs 3.37-3.43);
- sociability (paragraphs 3.44–3.46); and
- possession of a life (paragraphs 3.47–3.49);

***Ways of considering morally relevant features in different normative frameworks***

We then turn to the question of deciding how, with regard to the possible or certain benefits of research, such characteristics should be taken into account in moral decision making: through weighing of factors (for example, the degree of suffering experienced by animals versus the value of benefits of research) or through the generation of absolute prohibitions (for example, that no research should be undertaken on animals that are capable of higher cognitive capacities, such as the chimpanzees, regardless of the benefits; paragraphs 3.51 and 3.57). A consequentialist view weighs all costs against all benefits (paragraphs 3.52–3.55). A deontological view lays down particular prohibitions (paragraphs 3.56–3.57). A hybrid view contains some prohibitions and some weighing (paragraphs 3.58–3.61). Hybrid views appear to prevail in practice, both in UK regulations and in public attitudes.

Two questions are especially important in the context of hybrid views: first, what are the absolute constraints; and secondly, how are different morally relevant factors weighed within the permitted area? To answer these questions, we will always need to consider at least five questions (paragraph 14.3):

i) what are the goals of research?

ii) what is the probability of success?

iii) which animals are to be used?

iv) what effect will there be on the animals used in the experiment?

v) are there any alternatives?

***Assessing pain, suffering and distress***

Since the nature of any pain, suffering or distress that an animal might experience in scientific uses is crucial to assessing the ethical implications of research involving animals, we focus in Chapter 4 on the capacity of animals to experience such states, and on philosophical and practical problems in making such assessments.

We conclude that although philosophically it is extremely difficult to determine *exactly* the subjective experiences of animals, practically it is often straightforward to make meaningful approximations. The evaluation of clinical signs, the study of animal choices, familiarity with ethological and ecological data, and consideration of physiological and neurological features are all important (paragraphs 4.18–4.28). In the spirit of critical anthropomorphism therefore, consideration of scientific evidence, especially in relation to species-specific needs of animals, can be combined fruitfully with familiarity, empathy and methodological observation (paragraph 4.7 and 4.29–4.30). Nonetheless, care needs to be taken to avoid unwarranted anthropomorphism in applying terms such as pain, suffering and distress, which we use successfully in human–human interactions, to animals (paragraph 4.60).

In practice, the welfare implications for animals involved in research and testing vary greatly. Whether or not animals experience pain suffering and distress, either as a result of experimental procedures or in the wider context through breeding, transport or housing, depends on a number of factors. These include the nature of the experiment and the likely adverse effects that it may entail, standards of handling and husbandry, and the skills and motivation of those handling the animals to implement Refinements, such as in the use of pain relieving medicines or the provision of enrichments. While it is therefore impossible to generalise about the way animals are affected by research, we make some observations on the kind of factors that influence animal welfare in paragraphs 4.31–4.59. This information needs to be considered in relation to the specific uses of animals in different types of research, which are described in Chapters 5–9.

***Moral agency and the role of regulation***

We explore the question of what it means to be a moral agent. This concept is important in deciding what it is to be a morally responsible scientist or animal technician, and also what the role of regulation should be in generating an appropriate environment (paragraphs 3.69–3.77). We contrast two views:

- that to be a moral agent is a matter of following a set of rules or principles; and
- that the requirements of moral agency cannot be formulated in terms of a precise set of principles, but rather requires cultivating a certain set of dispositions of character, usually called virtues.

We conclude that some form of regulation is necessary for good moral practice, but that it is crucial to be aware that it may not be *sufficient* (paragraph 3.77).

***The views of the members of the Working Party***

There is no consensus within the Working Party as to whether one of the morally relevant features is a master property, nor whether a consequentialist, a deontological or a hybrid approach is the most appropriate framework for deciding whether or not a specific, or any, type of research is acceptable. The Working Party has therefore not been able to agree on a single ethical stance. Instead, we present an outline of four possible ethical positions that can be taken, which mark positions on a *continuum*:

- *The 'anything goes' view (paragraphs 14.16–14.20)*

  If humans see value in research involving animals, then it requires no further ethical justification (no member of the Working Party takes this position).

- *The 'on balance justification' view (paragraphs 14.2–14.27)*

  In accepting research involving animals one acts with full moral justification, while accepting that every reasonable step must be taken to reduce the costs that fall on animals.

- *The 'moral dilemma' view (paragraphs 14.28–14.40)*

  Most forms of research involving animals pose moral dilemmas: however one decides to act, one acts wrongly, either by neglecting human health and welfare or by harming animals.

- *The 'abolitionist' view (paragraphs 14.41–14.52)*

  There is no moral justification for any harmful research on sentient animals that is not to their benefit. Humans experiment on animals not because it is right but because they can (the 'weakness of morality' view, as a sub-category of the abolitionist view, is considered in paragraphs 14.52).

For each position we describe (i) the justification for using animals in research, (ii) the implications for using animals in research and in other contexts, (iii) the value attributed to research and (iv) the role of the Three Rs. The reader is invited to judge whether one or other of the positions is superior to others. In presenting them, we are clear that moral frameworks are not to be acquired and maintained in a simple 'pick and choose' fashion. Rather, they require continuous scrutiny and justification (paragraph 14.10).

Furthermore, all members agree that independently of morally relevant features such as sentience, higher cognitive capacities, capability for flourishing and sociability, the acceptance of even relatively mild experiments for great benefit depends on the acceptance of two vital moral assumptions: that the life of laboratory animals such as mice does not have *absolute value*; and that *forced consequentialist sacrifice* is acceptable. (By the latter term we mean to say that one is able to justify a morally unequal distribution of costs and benefits among different beings.) There is no consensus within the Working Party as to whether these assumptions are morally acceptable. However, all members do agree with the conditional: harmful research involving animals must be morally unacceptable if animal life is seen as having absolute value, or if forced consequentialist sacrifice is always seen as wrong (paragraph 14.6).

***Public policy in the context of moral disagreement***

As in the case of other ethically contentious issues, such as abortion or euthanasia, any society needs to settle on a single policy for practical purposes. Steps need to be taken to reduce as far as possible existing disagreement. At the very least, if a public policy is adopted that many believe to be morally wrong, it may lead to instability, protest and, in extreme cases, civil unrest.

We consider that the concept of the Three Rs, and the type of hybrid moral position underlying the A(SP)A (some absolute constraints, some balancing) could be accepted, or at least tolerated, by all those holding reasonable views. Clearly, neither the Three Rs nor the A(SP)A command universal respect, and hence it would be wrong to claim that these approaches could be supported fully from the positions included in the spectrum set out above. For example, abolitionists will not agree to any invasive research involving sentient animals, and hence will not be able to genuinely share a consensus permitting it under certain conditions. However, they may, in principle, be able to tolerate the approach of the Three Rs and the provisions of the A(SP)A as a *compromise*, while continuing to campaign for a change in policy. Thus, although it would be wrong to suggest that there can be a *substantive consensus* (i.e. consensus on a shared view that research can be viewed as justified), it seems right to say that in view of the current situation an enlarged *procedural consensus* is achievable (i.e. consensus that certain democratic procedures are justified, such as a system of licensing and control of animal research that is deemed necessary). By fine tuning the regulations, relaxing some restrictions and introducing others, a broader group of people could give a greater endorsement to the form and content of the regulations than has been the case so far, even if no one set of regulations would be considered fully acceptable by all (paragraph 14.59).

If this approach is to count as a fair process, several conditions need to be met.

- All involved need to be able to have access to relevant information about research involving animals, such as the goals, welfare implications and alternatives to research, in order to judge whether specific types of research are justifiable in respect of their normative frameworks.
- The discussion about appropriate policies must be conducted in a fair and informed manner, which permits all reasonable participants to argue their case. The use of violence and intimidation are highly damaging to this process and are unacceptable, as they erode the necessary climate for reasoned debate.
- There must be a genuine possibility for policies to be readjusted. For this to be achieved, there must be reliable evidence about the views of members of the public so as to judge whether specific policies need to be revised (paragraph 14.63).

## V. Conclusions and recommendations

Before we present the conclusions and recommendations of the Working Party, we must clarify two important points. First, members of the Working Party who believe that research using animals is, on balance, justified, as well as those members who take the view that it poses a moral dilemma, find most research which is currently undertaken to be acceptable. They are cautious of any proposals that might undermine progress in specific areas of basic and applied sciences which, they believe, depend crucially on research involving animals. Other members who, within the spectrum of possible views, are closer to the abolitionist view, are implacably opposed to the use of sentient animals for any scientific or medical purposes. They are equally cautious of any proposals that prolong or legitimise the infliction of pain and suffering on sentient animals. We emphasise that the recommendations that follow below, several of which aim to improve the conditions in which animals are used, should not be taken to imply the acquiescence of the latter group to animal experimentation. These members acknowledge that animals are currently subjected to experiments and believe that they need protection. While they continue to advocate that the recommendations should go further in specific areas, they accept them as steps in the right direction, without endorsing research involving animals in principle.

Secondly, as implied above, because of the diversity of views and beliefs held by the Working Party, it has not been possible to achieve complete agreement on all of the recommendations by all members of the group. In our discussions, however, and in discussion with the Council, it became clear that in the context of a highly polarised debate it is important to make

unambiguous recommendations in specific areas. While it is therefore not possible to attribute to all members of the group the conclusions and recommendations presented on any one issue, all members do accept the recommendations as valid contributions to the debate, clarifying further important implications of the more abstract thoughts presented in the consensus statement above. Nonetheless, on a few occasions it did not prove possible to identify positions that were acceptable to all members. In such instances we have tried to explain the areas of disagreement and we hope that these descriptions help to clarify the nature of the underlying dispute in a constructive way (paragraph 15.21).

***The Context of the debate***

*Statistical information about the number of animals used and the suffering involved*

The *Annual Statistics of Scientific Procedures on Animals*, published by the Home Office, have an important role in providing information about animal experimentation. At the same time, there is wide agreement that the data are presented in ways that are not readily accessible to lay people, and that the presentation could be improved. In particular, the Statistics have been criticised for not providing clear answers to the following questions: (i) what is the nature, level and duration of pain, suffering and distress actually experienced by animals used in the different kinds of procedures? and (ii) how many animals are used in procedures and related activities?

The terminology used to describe the severity of projects and individual protocols and procedures is not straightforward and therefore difficult for members of the public to understand. **We recommend that the annual *Statistics* should provide case studies of projects and procedures that were categorised as *unclassified, mild, moderate* or *substantial*. Case studies should also include examples of animals used over extended periods of time and should describe not only their immediate involvement in research but also the range of factors that influenced their life experiences, such as the conditions of breeding, housing and handling** (paragraph 15.29).

Information about the suffering that animals involved in procedures experience in practice is unsatisfactory. **We recommend that the Home Office should make retrospective information about the level of suffering involved during procedures publicly available. In gathering this information the Home Office should also obtain and make available, retrospectively, information about the extent to which the scientific objectives set out in applications have been achieved** (paragraph 15.28).

**The current system of severity banding for project licences and the severity limits for procedures should be reviewed, particularly the use of the *moderate* category which covers a wide range of different implications for animal welfare. For the general public, the category *unclassified*, which refers to protocols and procedures involving terminally anaesthetised animals, is too vague to be informative, and should be clarified** (paragraph 15.30).[3]

We realise that the system of collecting data about the numbers of animals used in research is very complex and that care needs to be taken to avoid making existing administrative processes more onerous. **Nevertheless, we think it highly desirable to present clearer information about how many animals of a particular species experience pain, suffering and distress, to what degree, and for how long. We therefore recommend that the *Statistics* be revised to provide this information, including details about the number of animals killed under A(SP)A Schedule 1** (paragraph 15.33).

[3] We note that some explanation can be found in the *Guidance notes* on the Act (Home Office (2000) *Guidance on the Operation of the Animals (Scientific Procedures) Act 1986* (London: TSO), p32, available at: http://www.archive.official-documents.co.uk/document/hoc/321/321.htm Accessed on: 4 May 2005. However, it is unlikely that members of the public will consult this document, and it is therefore important to clarify the terminology in appropriate places, for example in the *Statistics*.

*Balanced information: campaigning organisations*

We encourage animal protection groups and organisations representing those involved in research using animals to produce fair and balanced literature on this subject. This should include, among other things, detailed information about both the scientific benefits and the costs in terms of the implications for animal welfare. Similarly, the advantages and limitations of using alternative methods for research need to be discussed in a realistic manner (paragraph 15.40).

*Violence and intimidation*

The current climate in which animal research takes place has been influenced by several factors, including protests that often entail threats, harassment and violence (paragraphs 2.22–2.24). The effects of these actions have been highly disproportionate to the very small number of activists involved.

Those who promote violence and intimidation to pursue their case against animal research often attempt to justify their actions on the basis that they are liberating animals in much the same way as the Allies liberated Europe from the Nazis. They believe the democratic process is too slow, and moreover that the voting system is invalid, in that animals are disenfranchised. In the wake of their activities are others who would not themselves use violence but who are prepared to threaten it, persuading themselves that bullying is acceptable because it is aimed at people who are themselves bullying animals. If some of those engaged in the animal rights movement were able to force research abroad or prevent multinational companies from opting to conduct work in the UK, by means of militant actions, they would claim such outcomes as a victory.

**We conclude that all approaches based on violence and intimidation are morally wrong:** democracy is a precious achievement that allows conflict to be resolved without recourse to violence. It cannot permit exceptions where militant activities displace debate and consensus, otherwise anyone with any strongly held view would be able to prevail over the majority. The debate about research involving animals must be conducted in a reasonable and civilised manner. Aiming to force research out of the country through the use of violence and intimidation is no solution to the complex issues it raises (paragraph 15.50).

*Public debates and discussions in stakeholder fora*

Much can be learned from meetings which provide a forum for dialogue and allow members of the public to discuss their views with relevant experts. **We welcome provision in the Government's Science & Innovation Investment Framework 2004–2014 for a new grants scheme 'to build the capacity of citizens, the science community and policy makers to engage in the dialogue necessary to establish and maintain public confidence in making better choices about critical new areas in science and technology.'**[4] We are aware that the way the grants scheme is operated is currently being reviewed, and that Ministers may decide to allocate funding for prioritised areas. **In view of our observation about the need to improve the quality of the debate, and also the Governments discussion about research involving animals in the Science & Innovation Investment Framework programme**[5] **we recommend that funding should be provided by the Government to identify and carry out novel ways of achieving stakeholder engagement and public debate on issues raised by research involving animals. The Office of Science and Technology (OST) should liaise with the APC and the National Centre for the 3Rs (NC3Rs) to advise Ministers on areas of particular concern.**

4 See Science & Innovation Investment Framework 2004-2014, paragraph 21, available at: http://www.hm-treasury.gov.uk/media/33A/AB/spend04_sciencedoc_1_090704.pdf. Accessed on: 21 Apr 2005.

5 Science & Innovation Investment Framework 2004-2014, paragraphs 6.16-7.20, available at: http://www.hm-treasury.gov.uk/media/33A/AB/spend04_sciencedoc_1_090704.pdf. Accessed on: 21 Apr 2005.

In addition to public events, there are a number of *ad hoc* and permanent stakeholder groups that enable discussion among stakeholders. In our own debates, we realised the importance of having members who between them hold a broad spectrum of views on animal research. This approach allowed for comprehensive consideration of relevant arguments about specific areas of research. We encourage all parties to continue to take part in such fora (paragraph 15.45).

*Open laboratories*

In order to improve and sustain public trust, researchers in animal research facilities must find more ways to open themselves to dialogue. **We therefore recommend that those involved in animal experimentation should take a proactive stance with regard to explaining their research, the reasons for conducting it, the actual implications for the animals involved and the beneficial outcomes they intend for society.** These discussions should take the form of a two-way process, in which scientists not only inform the public about their research, but also listen to and understand concerns by members of the public (paragraph 15.52).

*Research on views of the public*

Accurate information about the current concerns of members of the public are important in considering whether or not policies on research involving animals are likely to be supported by the majority of the population. However, because of methodological constraints, opinion polls are often of limited use, and there is a lack of peer-reviewed research. **We therefore recommend that the Economic and Social Research Council (ESRC) and other relevant funding bodies provide funding for research to be undertaken on the knowledge, opinions and views of members of the public on animal research, and the underlying ways of reasoning.** Particular attention should be paid to the level and quality of information that participants have prior to, and while taking part in, the research, and to the ways in which provision of information affects individual responses (paragraph 15.46).

*Education*

Public debate would also be enhanced by educating young people about issues raised by research involving animals, presenting all sides of the argument. More balanced materials could make an important contribution to an improved understanding of the benefits and costs, to both humans and animals, of research involving animals, particularly for use in schools. **We therefore recommend that the UK Department for Education and Skills should commission an academic department of education, which does not have close links to pressure groups or to those involved in animal research, to produce suitable materials for use across the curriculum as appropriate, especially at Key Stages 2 and 3** (paragraph 15.41).

***Regulation***

*Cost-benefit analysis and moral agency*

The cost-benefit assessment is at the heart of the regulation of research on animals in the UK. There is sometimes the view that the assessment is only being carried out by the Home Office,[6] which 'tells the researchers what to do' once it has decided on whether or not a licence application fulfils the criteria of the A(SP)A and is therefore acceptable. The APC's 2003 Report *Review of cost-benefit assessment in the use of animals in research* observed that this interpretation would be simplistic, since a number of other individuals and committees are involved in assessing directly or indirectly the costs and benefits of a project. Furthermore, we

6 The Home Office Inspectorate carries out this assessment and advises the Secretary of State who takes formal responsibility for the granting of licences.

concluded that it would be wrong to perceive acting morally simply as following rules. Instead, active and continued scrutiny of the costs and benefits is required from all those involved, before, during and after research. This responsibility cannot be devolved to regulators, and, as the APC has emphasised, the system is also not intended to function in this way (paragraph 15.55). **We therefore welcome the APC's clarification and recommend that those involved in reviewing research proposals** (Fig 13.1) **at every stage prior to submission to the Home Office consider not only the scientific aspects, but also animal welfare in appropriate detail** (paragraph 15.56).

Good science and good animal welfare are closely interrelated, and it would be wrong for the scientific review process to ignore animal welfare issues. We are aware that many funding bodies recognise this fact. In addition to assessments by internal review boards, some, such as the Medical Research Council (MRC) and the Wellcome Trust, routinely invite external reviewers to comment on welfare issues and the way the Three Rs are considered in research proposals that involve the use of animals. However, **there is anecdotal evidence that this practice is not universal, and we strongly recommend that other funding bodies review their approach** (paragraph 15.56).

*Information about the cost-benefit assessment*

The APC's 2003 Report, *Review of cost-benefit assessment in the use of animals in research*, provides very useful information about the application of the cost-benefit assessment in practice.[7] The Report also observes that relevant information is spread across several different documents, and recommends that **'there is a need for an easy-to-use, comprehensive list of factors to be taken into account in assessing costs, benefits and scientific validity, that could guide researchers and others engaged in ethical review under the act, such as members of Ethical Review Processes (ERPs).'**[8] **We endorse this recommendation.** Since Ethical Review Processes (ERPs) should, ideally, also include lay people, it is important that this information is provided in a way that is accessible to non-experts. **Such a document would also be of use to the general public and the same information therefore should be provided in an accessible manner on the websites of the Home Office for the general public.** These materials should include specific case studies and also a summary of the *process* of how decisions are made in practice (paragraph 15.38).

*Information about licensed research projects*

We note that, following an announcement by the Government in 2004, the Home Office has made available the first anonymised information in the form of *Abstracts of Project Licences*[9] in January 2005. **We welcome the principle of publishing more information, and the decision to make it available in a searchable and publicly accessible database in due course.** We also note that the information provided in the first Abstracts varies in content, level of detail and style of presentation. We therefore **recommend that the current form of presentation be reconsidered, to ensure that, as far as possible, meaningful information about the following categories is provided:**

- **the goals and predicted benefits of research;**

7 The criteria for making cost-benefit assessments are discussed in Chapters 3 and 4 of the APC's Report (see especially Chapter 4, Boxes 4.4, 4.5 and 4.6); Animal Procedures Committee (2003) *Review of the cost-benefit assessment in the use of animals in research*, available at: http://www.archive.official-documents.co.uk/document/hoc/321/321.htm Accessed on: 4 May 2005.

8 Animal Procedures Committee (2003) *Review of the cost-benefit assessment in the use of animals in research*, p73, available at: http://www.archive.official-documents.co.uk/document/hoc/321/321.htm. Accessed on: 4 May 2005.

9 Home Office (2005) *Abstracts of project licences granted under the 1986 Act*, available at: http://www.homeoffice.gov.uk/docs4/abs_projectlicences0.pdf. Accessed on: 21 April 2005. The Home Office has previously released details of ten project licences under a Code of Practice which preceded the Freedom of Information Act 2000, see Box 13.4.

- **the probability of achieving these goals;**
- **the numbers and species of animals to be used, and an explanation of why they are needed at this stage in the project;**
- **what is likely to happen to the animals during the course of the project, including adverse effects from husbandry, supply, transport and procedures;**
- **what consideration has been given to the Three Rs to achieve all or part of the research objective(s), and how they have been applied;**
- **on what grounds possible alternatives have been rejected;**
- **source(s) of funding (i.e. public, private or both) (paragraph 15.35).**

Members of the Working Party were unable to agree in which form this information should be provided. While there was a range of views, the ends of the spectrum were (i) that full project licences should be made available, in which only the names of researchers, research facilities and commercially sensitive information has been removed and (ii) that the current format, in amended form, is suitable, but needs to be kept under close review, as it may conflict with safeguarding commercial and academic competitiveness and confidentiality, and the safety of researchers working with animals (paragraph 15.36).

***Development and implementation of the Three Rs***

*Increased information about the Three Rs in journals*

In order to improve knowledge about and awareness of the Three Rs **we recommend that all journals publishing results of research involving animals consider the inclusion of a category on the Three Rs in the methodology section.**[10] Many journals now also provide supplementary information for articles on websites, and further details about the implementation on Three Rs could be provided in this way (paragraph 15.58).

*Coordination of efforts between funding bodies and the NC3Rs*

Medical research charities and research councils fund a large amount of animal research and should be encouraged to take more responsibility for the promotion and implementation of the Three Rs. Further to recommending that external reviewers comment on the way the Three Rs have been implemented in funding proposals (paragraph 15.56), we consider that those who fund research have two additional responsibilities. **First, in order to improve a systematic application of the Three Rs, funding bodies should request that for each project that receives funding, a short summary be submitted to the NC3Rs which describes the way in which the Three Rs were implemented in the project, which obstacles were encountered and how they might be overcome in the future.** This information would be useful to the NC3Rs in promoting exchange of experience and fostering best practice. **Secondly, based on this information, and in consultation with the NC3Rs, funding bodies should encourage funding applications for Three R-related research in areas that pose challenges (paragraph 15.59).**

*Enhancing the role of the ERP*

The ERP has the potential to make a greater contribution to the identification, promotion and implementation of the Three Rs and could play a more proactive role in identifying best practice and

[10] In a different context, one journal has recently reviewed its policy on the provision of information about statistical methodology in published articles. Research had revealed that this information was of varying quality, and the editors therefore decided to introduce a requirement for authors to submit specific information about statistical methods used in the methodology section of each article, see Editorial (2005) Statistically significant *Nat Med* **11**.

helping to facilitate exchange of information. We acknowledge that some organisations, particularly the Laboratory Animals Science Association (LASA) and the Royal Society for the Prevention of Cruelty to Animals (RSPCA), have organised meetings for ERP members in the past to assist this process. We support this approach and **recommend that these two organisations, together with other stakeholders where appropriate, identify a systematic and sustainable strategy to ensure that the ERP contributes most effectively to developing best practice in the Three Rs** (paragraph 15.60).

*Examination of new technologies for replacement potential: Chair of the Three Rs*

We have described the complex interplay leading to the development of Replacements in Chapter 11. Strategic examination of new scientific technologies for Replacement potential, their adaptation for general use and transfer of the technology could help to ensure further progress. Scientists working in basic research who develop new methods for specific research questions often do not have the Refinement, Reduction or Replacement of animal experiments as their main objective and tend not to adapt or promote new methods for this purpose. Much more 'horizon scanning' is needed. The Working Party has therefore considered whether it would be useful to institute at least one Chair of the Three Rs, to undertake research on new technologies for Refinement, Reduction and Replacement potential and to encourage students to carry out research with an emphasis on alternative methods. Several issues would need to be assessed in more detail before such a proposal could be developed further. First, the relationship of the Chair to existing initiatives and organisations that seek to promote the Three Rs would need to be clarified, to avoid duplication of effort, and to ensure that funds to promote the Three Rs are spent most effectively. Secondly, the exact profile of the Chair would need to be carefully designed to assess whether it would be more appropriate to focus the review of the wide range of new technologies in different areas of research on one of the Three Rs only, for example on Replacement. We have therefore not been able to agree on whether or not a Chair would advance and contribute to increased implementation of the Three Rs. However, **we consider that, in consultation with the NC3Rs, it would be of value if the MRC, the Wellcome Trust and other major funders of research review and explore further the proposal of establishing and funding such a Chair (paragraph** 15.61).

*Thorough analysis of scientific barriers to Replacements*

Difficulties in relation to implementing Replacements are sometimes cited to dismiss further consideration of the concept as unfeasible, regardless of the exact objectives of a particular research project. Some of those opposed to research involving animals also claim that a far wider range of research than is commonly assumed could be replaced by alternative non-animal methods, if there was sufficient will to do so (paragraph 11.3). In order to make further progress in the development and the implementation of Replacements, and in order to address the range of associated expectations it would be desirable to undertake a thorough analysis of the scientific barriers to Replacement and how they might be overcome. This task cannot be addressed in general terms, but requires an in-depth analysis of specific projects in particular areas of research. Since the unavailability of non-animal methods plays a central role in the cost-benefit assessment carried out under the A(SP)A,[11] **we recommend that Ministers request the APC to undertake or commission such an analysis for a series of projects with a wide range of scientific objectives**. A clear exposition of obstacles, and strategies for overcoming them would, first, allow research efforts to be focused on problems that must be overcome if animals are to be replaced for a particular purpose. Secondly, such an analysis would identify publicly the scientific problems which are thought to be insurmountable (paragraph 15.62).

11 See Home Office *Animals (Scientific Procedures) Act 1986*, Section 5 (a), available at: http://www.homeoffice.gov.uk/docs/animallegislation.html. Accessed on: 11 May 2005.

***Other issues***

*Motivating and monitoring Reduction of research involving animals*

One way of motivating and monitoring reduction of animal experiments would be to set *targets*. The most radical form of target would be to aim to abandon or phase out a specific area of animal experimentation. Members of the Working Party disagree about the setting of targets. Those who favour the approach argue that without targets there tends to be drift and fatalism (paragraph 15.65). Those who have major reservations question the feasibility of the approach and assert that those accountable can be unfairly held responsible for unrealistic expectations (paragraph 15.66).

We accept that setting targets is not straightforward:

- We welcome the concept of targets as a useful and universally used means of measuring progress towards specific aims. But we also see problems in applying such a strategy to research involving animals, where, in many cases, the setting of specific quantitative (numerical) targets is felt by those using animals in research to be unhelpful. Instead, we suggest that Reduction could be encouraged and monitored by means of a more flexible approach. One way would be to consider qualitative *markers of reduction*, for example, aimed at reducing research that causes substantial suffering. **The Government's Inter-Departmental Group on the Three Rs should undertake or commission a feasibility study to identify which kinds of reduction marker could be set in particular areas of applied and/or basic research.**
- In principle, reduction markers should only be set if they can be linked to a realistic strategy for developing the necessary Replacement methods that will not compromise the amount and quality of basic and applied biomedical research and testing that would otherwise be licensed by the Home Office. Reduction markers that 'ration discovery' are not compatible with the scientific approach.
- The development of any strategy should primarily be the responsibility of legislative bodies and governments, as should the task of providing the infrastructure and some of the funding to facilitate the process, in close consultation with stakeholders from academia, industry and animal protection groups.
- In implementing reduction markers it is crucial that initiatives at the national level are complemented, although not limited by, initiatives at the international level (paragraph 15.67).

*Duplication of research*

Another area where there may be potential for reduction concerns the avoidance of duplication of research or testing (paragraphs 12.6 and 15.16). There is a range of views about whether or not research is duplicated frequently (paragraph 15.69). However, we have not explored in this Report the question of the extent to which duplication occurs, or the feasibility of devising mechanisms that help to avoid the duplication of research. But we are clear that, in principle, duplication of harmful research is unacceptable (paragraph 15.16) and we therefore welcome the approach underlying the UK Government's Inter-Departmental Data Sharing Concordat (paragraph 12.6). The Concordat has recently been reviewed by the Government who commented that the agreement had ensured that 'regulators promote data sharing within the scientific community', noting also that there was no evidence that duplication was 'a significant problem in the UK'.[12] The Working Party has not been able to study the review, and

12 Home Office (2005) *Ministerial Response on the Report by the Animals Procedures Committee – Review of Cost Benefit Assessment in the use of animals in research*, p10, available at: http://www.homeoffice.gov.uk/docs4/jw280305flint_banner_report_by_the_animal_procedures_committee.pdf. Accessed on: 21 April 2005.

is hence not in a position to comment on the Government's view.[13] We also note that the APC welcomed the Concordat in its 2003 Report *Review of Cost-Benefit Assessment in the Use of Animals in Research*[14] but cautioned that it is not yet clear how effective it will be in preventing duplication of animal studies. In particular, the APC was concerned about the voluntary nature of the Concordat, and considered whether more binding measures, such as legislation, will be needed to achieve the Concordat's aims. **We endorse the APC's conclusion that the operation and effectiveness of the Concordat should be monitored carefully and reports placed in the public domain.** The Concordat will be reviewed again in 2006. Depending on the outcome of the reviews,[15] Ministers should explore whether it would be useful to request the APC to undertake a systematic study addressing in more detail specific issues raised by the possible duplication of research. Such a study could complement and develop further the review of the Concordat (paragraph 15.70).

*The scientific validity of animal research and the use of animals in the study of human disease*

The question about the scientific validity of animal experimentation for medical purposes is often confused with questions about complex ethical issues. Separation of scientific and ethical questions is essential if greater clarity is to be achieved in the debate about animal research. At present, there is a relatively limited number of useful systematic reviews and meta-reviews that address the question of the scientific validity of animal experiments and tests. **In principle, it would therefore be desirable to undertake further systematic reviews and meta-analyses to evaluate more fully the predictability and transferability of animal models (paragraph 10.39). We recommend that the Home Office in collaboration with major funders of research such as the Wellcome Trust, the MRC, the Biotechnology and Biological Sciences Reserach Council (BBSRC), animal protection groups and industry associations such as the Association of the British Pharmaceutical Industry (ABPI) should consider ways of funding and carrying out these reviews. In devising a strategy, priorities should be identified which, in order to respond to concerns of the public, consider, among other things, the validity of research that falls in the substantial category and research that involves primates** (paragraph 15.80).

*The use of genetically modified (GM) animals in basic research*

Specific problems in relation to assessing welfare may be raised by relatively novel ways of producing animals, such as genetic modification or cloning. We take the view that the focus of concern, in the case of all deliberate attempts to influence the genetic basis of animals, should be on the welfare implications in terms of the likely pain, suffering or distress.

Documentation of the phenotypic outcomes of genetic modification (i.e. documentation about the way in which animals are affected) can facilitate the future monitoring and assessment of welfare implications experienced by animals produced in the context of 'forward' or 'reverse' genetics (paragraph 5.23). **A systematic approach to the description of GM phenotypes is crucial for assessing and monitoring welfare implications, and for undertaking thorough cost-benefit assessments**. For this reason, **we recommend that more efforts should be made to establish**

13 Parliamentary Under Secretary of State Caroline Flint commented in the Government's response of 28 March 2005 to the APC's Report on the cost-benefit assessment that 'the outcome of the review' would be published as an Annex to the Minutes of the Inter-Departmental Group on the Three Rs, see Home Office (2005) *Ministerial Response on the Report by the Animals Procedures Committee – Review of Cost Benefit Assessment in the use of animals in research*, p10, available at: http://www.homeoffice.gov.uk/docs4/jw280305flint_banner_report_by_the_animal_procedures_committee.pdf. Accessed on: 21 April 2005. However, the Working Party was not able to consider this document before finalising this Report.

14 Animal Procedures Committee (2003) *Review of cost-benefit assessment in the use of animals in research*, p52, available at: http://www.apc.gov.uk/reference/costbenefit.pdf. Accessed on: 4 April 2005.

15 See footnote 14.

**comprehensive ontologies**[16] **in the form of databases for GM animals. These databases should not be restricted to the receipt and dissemination of phenotypic information relevant to the scientific objectives of the research, but should also provide detailed description of associated implications for welfare. Established central databases such as the Mouse Genome Database (MGD) in the USA**[17] **should be used as the primary mechanism for archiving and distributing information on GM animals**. The information should be made available on freely accessible websites for the use of the scientific community and interested lay people (paragraph 15.73).

It is also important to continue to investigate and improve current methods for assessing the phenotypic and welfare status of GM animals. Any terminology and ontology for describing specific welfare implications should be integrated with the emerging phenotype ontologies. We note that current welfare-assessment systems vary with regard to the amount of information and the degree of detail being made available. **We recommend that the NC3Rs should consider this variation with a view to advising on the rationalisation and development of phenotype and welfare ontologies and their interrelationships** (paragraph 15.74).

**We also recommend that scientific journals require the submission of phenotype and associated data about welfare to databases as a condition of acceptance of submitted papers.** Although scientists often routinely submit information about new phenotypes to databases such as MGD, a more systematic approach would be useful in promoting the availability of information about both the phenotype and the implications for welfare, which would help avoid duplication and improve welfare management. Data should be provided according to the requirements of the standardised transgenic mouse nomenclature (paragraph 15.75).[18]

*Toxicity testing*

Current trends in society suggest that there is an increasing intolerance to risk, although some commentators believe we are now over-zealous in testing requirements. We described the types of procedures typically undertaken in toxicology research in Chapter 9. In view of the severity that some toxicity testing can entail, **we endorse the recommendation of the House of Lords Select Committee *Report on Animals in Scientific Procedures* (2002) that 'the government and the scientific community should engage more in a systematic and visible search for methods involving the Three Rs in toxicology. The Government should nominate one department to take the lead in this.' We recommend that the Inter-Departmental Group on the Three Rs should coordinate this work** (paragraph 15.81).

With regard to international initiatives the Working Party is concerned about the potential impact of recent European Union (EU) legislation for new and existing chemicals testing (Registration, Evaluation and Authorisation of Chemicals, REACH), which is likely to be implemented by 2006. According to some estimates, had the initial proposal been implemented, up to 12.8 million animals could have been involved for the testing of approximately 30,000 existing chemicals (Box 9.2).[19] The conclusion that the scale of testing and use of animals did not appear to justify the additional protection afforded to society has been widely supported, and discussions about the actual implementation were still in progress at the time of writing. Whatever its final form, REACH will greatly increase animal testing across the EU. While we make no detailed recommendation in

16 An 'ontology' in this context is an explicit formal specification of terms and the relationships among them, used to underpin the construction and querying of databases.

17 See Mouse Genome Informatics (MGI) available at: http://www.informatics.jax.org. Accessed on 21 April 2005.

18 See Mouse Nomenclature Home Page, available at: http://www.informatics.jax.org/mgihome//nomen/index.shtml. Accessed on 21 April 2005.

19 Institute for Environment and Health (2001) Testing requirements for proposals under the EC White Paper – Strategy for future chemicals policy; available at: http://www.le.ac.uk/ieh/webpub/webpub.html. Accessed on 21 April 2005.

this area, it is crucial that new approaches to risk assessment that implement the Three Rs most effectively should be explored, particularly by making maximum use of data sharing and using computational and *in vitro* tissue culture methods where possible (paragraph 15.82).

*The international context of animal research*

Many tests involving animals are conducted to provide safety or efficacy data for regulatory authorities, in compliance with national or international legislation. Thus, if various authorities require testing to be carried out using different study designs, a single chemical that is marketed in a number of countries might need to be tested several times. Harmonisation of test guidelines, so that a single study design is acceptable to regulatory authorities in many countries, is a very valuable means of reducing the use of animals in safety and efficacy testing. The International Conference on Harmonisation (ICH) has managed to improve mutual acceptance for the pharmaceutical industry, but much still needs to be done to extend this approach to other product areas (paragraph 15.84). Increased efforts must be made to standardise and harmonise testing requirements, in order to ensure that the minimum number of animals is used at the global level. **We therefore recommend that the UK through its National Coordinators at the Organisation for Economic Cooperation and Development (OECD) makes it a priority to identify areas in which harmonisation continues to be difficult and initiates steps to increase adoption of scientifically valid protocols that entail the least adverse welfare costs to the animals involved.** We also note that under the Inter-Departmental Concordat on data sharing, regulatory authorities aim to 'press for agreement on behalf of the UK Government for fullest provisions and procedures which enable data sharing when negotiating, updating and transposing relevant European Directives and when taking part in other international harmonisation processes.' **In order to support the proposed initiative by the National Coordinators at the OECD, we recommend that the UK Inter-Departmental Group on the Three Rs should produce or commission a report on cases where less severe protocols are not recognised internationally, whether for scientific or other reasons, and make suggestions for improving acceptance** (paragraph 15.86).

International guidelines also have a crucial role with regard to welfare standards of animals involved in research. There is evidence that relevant OECD guidelines do not use important concepts such as what defines a *maximum tolerated dose, severe distress, obvious pain* or a *moribund condition* consistently. Several of the existing OECD test guidelines could also be improved with regard to issues such as environmental enrichment, and conditions of housing, as, for example, some do not specify the requirement for group housing where this would be possible. All these factors can act as potential sources of avoidable suffering for the animals, and **we recommend that the OECD review and revise relevant guidelines to achieve greater consistency and to contribute to a wider application of the Three Rs in view of current knowledge (paragraph 15.87).**

*UK researchers commissioning or undertaking research or testing abroad*

There are a number of scientific, Three R-related and logistical reasons why researchers may collaborate with overseas scientists, outsource research work or obtain animals or animal-derived products (such as monoclonal antibodies) from other countries. This interaction can provide a useful means of disseminating good practice developed within the UK. But there is also a need to ensure that the international nature of research is not used to introduce double standards. **We note the position statement by the Wellcome Trust, which, as a general rule, we endorse:**

> 'International research supported by the Trust is expected to be carried out in the spirit of the UK legislation as well as being compliant with all local legislation and ethical review procedures.'[20]

20 The Wellcome Trust *Policy on the use of animals in medical and veterinary research*, available at: http://www.wellcome.ac.uk/doc%5Fwtd002764.html. Accessed on 21 April 2005.

Further to the requirement implied in this statement, some members of the Working Party would like to see formal provisions in place which ensure that research and testing, both nationally and internationally, is always carried out in accordance with the least-severe protocols, in order to minimise harm to animals used in research. They would also welcome the introduction of regulations that would prevent UK researchers from importing or outsourcing research or research products that it would not be possible to obtain in the UK. Other members of the group, while welcoming the aspiration behind such proposals, have reservations about their appropriateness and feasibility. Members also differ in their views as to whether UK-based research is being driven abroad because of the current, or likely future, regulatory provisions and practice. Despite these disagreements, all members of the Working Party emphasise that maintaining high standards in the UK has the potential to continue to influence regulations positively elsewhere. At the same time, the provisions of the A(SP)A and their implementation also need to be reviewed regularly in the context of national and international developments in policy and public debate (paragraphs 15.88–15.91).

# Section 1

## Introduction and context

# Chapter 1

## Introduction

# Introduction

## Research involving animals: outline of the controversy

1.1 Humans have a variety of different relationships with animals. They bring pleasure to our lives as companions, and when we observe them in their natural environment, or in zoos and wildlife parks. In some cultures, certain animals are thought to have religious significance and are treated with special reverence. But we also use animals extensively for food, clothing, transport and sports such as racing or hunting.[1] Animals are sometimes culled to maintain stable populations in natural ecosystems, or killed when they come into conflict with humans. For example rats, flies and mosquitoes are generally considered to be pests. These examples show clearly that the relationships between humans and animals differ in terms of the benefits they bring to humans, and their effects on the welfare of the animals. This Report focuses on an examination of the ethical issues raised by the use of animals in one particular area: basic and applied scientific and medical research.[2]

1.2 Debate about research on animals is not new. Animals have been used in basic and applied research for more than 2,000 years and the acceptability of this practice has been contested for a similar length of time (paragraph 2.6). During the last century, the technological capacity of the medical, biological and pharmaceutical sciences has developed substantially and both the number of researchers and the number of animals used in research have increased. In recent years the debate has intensified and has become more public in several countries.[3]

### Box 1.1: Use of the term 'animal'

Strictly speaking, it would be more appropriate to use the terms 'human animals' and 'non-human animals' (and likewise 'human primates' and 'non-human primates') to distinguish between humans and other animals. According to systems of biological classification, humans are within the animal kingdom and belong to the taxonomic group referred to as primates. However, for reasons of brevity, the term 'animals' is used to refer to 'non-human animals' throughout this Report. This use should not be taken to imply differences between humans and animals in their ability to suffer or feel pain to an extent that sets humans apart from all other species. Neither should it be taken to imply differences in moral status.

1.3 There is a wide range of opinions concerning the acceptability of research involving animals. It is unhelpful to describe the debate as being only between those who are in favour of research and those who are against it. A very brief overview would need to include at least the following range of views. Most medical research charities, many patient groups, the current UK Government and most members of the scientific community emphasise the scientific and medical benefits that have resulted from animal research. They stress that it has made a substantial contribution to our understanding of biological processes, and that it has been responsible for many crucial biomedical advances. Historically, the discovery of the circulation of blood, the function of the lungs, and the hormonal system in humans has involved research on animals. More recently, the development of important therapies and preventative treatments, including antibiotics, insulin, vaccines, organ transplantation and modern medicines, has involved animal research and testing. Moreover, such research has begun to provide critical insights into some of the more complex diseases, such as cancers,

1 For a brief statistical overview of the numbers of animals used in different contexts see Appendix 1 and see Appendix 2 for information about the numbers of animals used in scientific procedures.

2 In this report, we generally use the term 'research' in a broad sense, encompassing experiments undertaken in basic and applied research, as well as for the purpose of toxicity testing. We use the term 'testing' to refer exclusively to toxicity testing.

3 A recent survey in China, South Korea and Vietnam commissioned by the International Fund for Animal Welfare concluded that 77–90% (variation across different countries) of people believed 'we have a moral duty to minimise suffering', when asked about their views on the treatment of animals. MORI 2005 *Asian Nations Share British Concern for Animals*, available at: http://www.mori.com/polls/2005/ciwf.shtml. Accessed on: 6 Apr 2005.

heart disease, depression, human immunodeficiency virus (HIV), malaria and tuberculosis. Farm animals and pets have also benefited from the development of new veterinary medicines and vaccines.[4] Those who support research involving animals argue that on both ethical and scientific grounds, it is necessary for such research to continue.[5]

1.4 Others also drawing on ethical and scientific arguments object to this conclusion.[6] Campaigning organisations, with support from some scientists, question whether the results of experiments undertaken on animals can be reliably applied to humans.[7] They argue that animal research is too often perceived as the only means of addressing specific research questions, that scientists are reluctant to explore other methodologies and that more effort should be made in exhausting the potential of alternative scientific methods. They also question whether it is right for humans to subject animals to procedures that cause pain and suffering, and from which they will not benefit. Accordingly, some commentators take the view that all animal research should be abandoned immediately.[8]

1.5 A range of further positions can be found in the debate. Many people may have sympathy for some assumptions, but reject others made by those taking the two positions sketched above. For example, some accept the basic scientific validity and necessity of animal research, but question whether enough effort is made to reduce the suffering of the animals involved. Others object to specific kinds of research, and have concerns about the species used, or the aims of the research. There are also those who, in wishing for an end to all research on animals, acknowledge that a sudden abandonment is not straightforward. For them, a phasing out of all such research, combined with maximum efforts to reduce any pain, suffering or distress that animals might experience, is a highly desirable goal.

## Types of research and numbers of animals used

1.6 Research involving animals is varied in both its nature and purpose, in the types of animals involved and in the effect that it has on them. At its least harmful, it takes the form of passive observations of wild animals in their natural habitats. Scientists also observe animal behaviour under laboratory conditions. Such studies may have a negative impact on the animals' welfare if they are kept in an environment that is incompatible with their species-specific needs. Certain invasive laboratory techniques may affect the welfare of animals in relatively mild ways. For example, some pharmaceutical research requires the repeated taking of blood samples. More harmful research, such as testing the safety of novel medicines (toxicology), may cause substantial pain and suffering. Almost all laboratory animals are killed once experiments are complete; in some cases research is undertaken on anaesthetised animals that are killed before they recover consciousness. In the UK, any 'procedures' involving vertebrates (and the common octopus) that may cause 'pain,

4 For 2003, 150,679 procedures in the category *Applied studies – veterinary studies* were recorded, comprising 5.4% of the total number of procedures and 5.5% of the total number of animals. Of the total number of procedures in this category, the farmed animals pigs, sheep, cattle, poultry and fish accounted for 79%. Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (London: HMSO).

5 See, for example, websites for: the Coalition for Medical Progress, available at: http://www.medicalprogress.org/; The Association of Medical Research Charities (AMRC), available at: http://www.amrc.org.uk/; UK Home Office Animals in Scientific Procedures, available at: http://www.homeoffice.gov.uk/comrace/animals/index.html; RDS Understanding Animal Research in Medicine, available at: http://www.rds-online.org.uk. All accessed on: 21 Feb 2005.

6 In this Report, the terms 'ethics' and 'morals' are used synonymously. For further discussion see Crisp R (1998) Ethics, in *Routledge Encyclopedia of Philosophy*, Craig E (Editor) (London: Routledge), available at: http://www.rep.routledge.com/article/L132. Accessed on: 23 Mar 2005.

7 See British Union for the Abolition of Vivisection (BUAV) *Frequently asked questions about vivisection*, available at: http://www.buav.org/faqs.html#faq13. Accessed on: 23 Mar 2005.

8 A very small group of those opposed to the use of animals also protest by damaging property and by using violence against individual researchers, institutions and business partners, paragraphs 2.22–2.24 and 15.47–15.50.

suffering, distress or lasting harm' must be licensed by the Home Office. The term 'procedure' is a technical term that covers more than just the conditions entailed by an experiment (or series of experiments). Procedures also include specific conditions relating to the breeding, handling and housing of laboratory animals that may affect their welfare.

1.7 Estimates of the total number of animals used annually in research around the world are difficult to obtain and range from between 50 to 100 million animals.[9] In the UK, approximately 2.72 million animals were used in scientific procedures during 2003.[10] Thirty years ago, twice as many animals were used. However, it is widely expected that advances in genetic research will reverse this decline and lead to a renewed increase in the coming years, mainly in the use of rodents (see paragraph 5.23).

## Issues raised by specific types of animal research

1.8 Two questions are fundamental to the debate about research involving animals. First, does the scientific use of animals lead to valid, useful and relevant results in specific areas? Secondly, is it permissible for one species to cause pain, suffering and death to another to achieve aims that primarily benefit the former species? In order to consider these questions, we must explore a number of complex issues. These include a discussion of the arguments about the moral status of humans and animals, and ways of morally justifying specific kinds of treatment. The usefulness and relevance of the different kinds of research in which animals are involved need to be examined, as well as the degree of pain and suffering which they may experience in research.

1.9 It is unhelpful to consider these issues merely in the abstract. Rather, it is necessary to examine the types of research that give rise to particular concerns and we briefly consider four examples. First, knowledge about the genetics of animal traits enables researchers to 'design' animals with specific features, using different methods of genetic modification (GM). Some people perceive such activities as an instance of increasing commodification of animals. Critics of the GM approach are also concerned about the large numbers of animals (mostly rodents) required to produce GM strains and the fact that the welfare implications of genetic modification are often unforeseeable (see Chapters 4, 5 and 7).

1.10 The second example concerns the use of animals as models for human disease. In the case of hepatitis C, in the 1980s researchers infected chimpanzees in order to understand the pathology of the disease and to develop a vaccine (see Chapter 6). Researchers have also bred or created by other means animals that are affected by particular diseases so that they can study the processes involved, and develop possible interventions. These models include mice with diseases such as cystic fibrosis, rheumatoid arthritis (RA) or transmissible spongiform encephalopathies (TSEs) such as BSE (Bovine Spongiform Encephalopathy, see Chapters 6 and 7). Many people object to the idea of producing animals that will exhibit the symptoms of a serious disease, whether by selective breeding, genetic modification or other means.

1.11 Thirdly, experiments on animals that, in evolutionary terms, are most closely related to humans, such as primates, have been particularly controversial. They are used in many areas of neurobiology because their brains share a great number of structural and functional features with human brains (see Chapter 5 and 6). While this similarity has scientific

9 Orlans FB (1998) History and ethical regulation of animal experimentation: an international perspective, in *A Companion to Bioethics*, Kuhse H and Singer P (Editors) (Oxford: Blackwell), p400.

10 See Appendix 2 and Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (London: HMSO). The *Statistics* give details about all animals used under the Animals (Scientific Procedures) Act 1986 (A(SP)A), i.e. all living vertebrates and members of the *Octopus vulgaris* (common octopus) species used in research. They do not include animals that are outside of these categories, such as insects.

advantages, it poses some difficult ethical problems, because of an increased likelihood that primates experience pain and suffering in ways that are similar to humans.

1.12 Fourthly, the use of animals for toxicity testing in the development of pharmaceuticals and non-medical products such as agricultural and household chemicals has attracted criticism with regard to the degree of pain and suffering that is involved, and the numbers of animals killed. Some opponents of this type of animal use also consider that the scientific validity of such tests is doubtful (see Chapters 8–10).

## The context of the debate

1.13 Debate about the value of research on animals and the degree of suffering involved is often influenced by the media. Some people take a positive view, believing that reporting by the media has contributed to a more focused and factual debate about the costs and benefits of animal research. For example, the role of animal research in the development of new treatments for diseases has been explained in a wide range of newspaper reports. Others think that publication of the findings of undercover investigations in animal research laboratories have been a useful complement to the public debate, by showing how animals are affected (see paragraphs 2.19–2.21). However, the media are also occasionally responsible for sensationalist items of news that either exaggerate the likely medical benefits of animal research or the suffering caused to animals. There are fears that such reporting could lead to further unhelpful radicalisation and polarisation of the debate.

1.14 Assessing the views of the public about research on animals is difficult. The evidence from surveys of public opinion is inconsistent. According to an opinion poll commissioned by *The Guardian* newspaper in 2001 that asked 1,004 adults their views on a range of issues, 46 percent of respondents supported the use of animals in the scientific testing of new medicines for humans, 36 percent were opposed and 18 percent were undecided.[11] By contrast, in 2003, a poll commissioned by the British Union for the Abolition of Vivisection (BUAV), carried out by TNS, found that 76 percent of respondents said that, as a matter of principle, they opposed experiments on any animals which caused pain, suffering, distress or lasting harm.[12] A Market & Opinion poll Research International (MORI) poll commissioned by the Coalition for Medical Progress in 2002 suggested that 90 percent of the UK population were willing to accept animal research, provided that certain criteria relating to the research objectives and the degree of animal suffering were met. This poll also found that 35 percent of the UK population did not support any kind of animal research because of implications for welfare, that 21 percent wished for a government ban on all kinds of animal research and that 61 percent of all respondents wanted to know more about research involving animals before forming a firm opinion.[13]

1.15 Inconsistent views about animal research that are revealed in opinion polls may illustrate that people often hold conflicting views simultaneously. Surveys are also relatively superficial in their attempts to evaluate what are often complex ways of reasoning. It is therefore important to distinguish between opinion polls, which commonly fulfil the role of

11 ICM (2001) *The Guardian/ICM Monthly Poll*, available at: http://www.icmresearch.co.uk/reviews/2001/guardian-poll-jan-2001.htm. Accessed on: 7 Apr 2005.

12 BUAV (2005) Press release *Government in ruse to thwart Freedom of Information Act*, available at: http://www.buav.org/press/2005/01-01.html. Accessed on: 7 Apr 2005.

13 MORI (2002) *The Use of Animals in Medical Research*, Research Study Conducted for The Coalition for Medical Progress, p24, available at: http://www.mori.com/polls/2002/pdf/cmp.pdf. Accessed on: 7 Apr 2005. See also MORI (1999) *Attitudes Towards Experimentation on Live Animals*, commissioned for *New Scientist,* available at: http://www.mori.com/polls/1999/ns99038t.shtml. Accessed on: 7 Apr 2005; MORI (1999) *Animals in Medicine and Science*, General Public Research conducted for Medical Research Council, available at: http://www.mori.com/polls/1999/pdf/mrc99.pdf. Accessed on: 7 Apr 2005.

market research, and academic research, which is usually better suited to analysing the subtleties of peoples' views and opinions. Methodology and findings of opinion polls are not normally subject to academic peer review, and the results of polls frequently appear to correlate with the views of the organisations that commission them.[14] Despite their limitations, results from opinion polls are widely cited and treated authoritatively. For example, MORI's finding that 90 percent of people in the UK accept animal research under certain conditions has been quoted extensively in the media. It has also been referred to by several organisations, and the UK Government, without further qualification.[15]

1.16 Opinion polls should in general be treated with caution.[16] There is little recent peer-reviewed research that would allow a reliable assessment to be made of public opinion on animal research. One recent study, based on focus groups, indicated that participants were caught in a moral dilemma by wishing to maximise both animal welfare and human benefits in research on animals. Most people preferred not to confront the issue, although there appeared to be acceptance of animal suffering when there was a genuine human need, typically expressed in developing cures for life-threatening diseases.[17]

1.17 This Report does not seek to summarise public opinion or derive conclusions from it. While we have conducted a wider Consultation (see Appendix 5) and have additionally considered facts and opinions from a range of external experts (see Appendix 4), our primary aim has been to undertake a thorough qualitative analysis of the scientific and ethical issues. The value of this examination does not depend on support from particular professional, political or social groups, but on the clarity and force of the arguments.

## Structure of the Report

1.18 The Report focuses on ethical issues arising from the fact that animals are used by humans for research in ways that may cause pain, suffering or death. This is a substantial task. We have therefore avoided extending our terms of reference to more specific issues, such as the use of animals in education and training, issues raised by the unintended release of GM animals into the environment, the patenting of animals, and xenotransplantation.[18] We begin in Chapter 2 by providing a brief overview of the historical, and current social and

14 In a recent study that reviewed 56 surveys on how people view the use of animals in research, the authors concluded that there were marked discrepancies in the results reported in different surveys. See Hagelin J, Carlsson H-E and Hau J (2003) An overview of surveys on how people view animal experimentation: some factors that may influence the outcome *Public Understand Sci* **12**: 67-81. The design of the 2002 MORI poll mentioned above has been criticised by the BUAV. See BUAV (2004) Press release *New survey shows that doctors do not share government support for animal experiments*, available at: http://www.buav.org/press/2004/09-01.html. Accessed on: 7 Apr 2005.

15 See, for example, the website of the Coalition for Medical Progress, which commissioned the research, available at: http://www.medicalprogress.org/reference/mori.cfm; The Bioscience Innovation and Growth Team (BIGT) (2003) *Bioscience 2015*, p22, available at: http://www.bioindustry.org/bigtreport/; Home Office, Attorney General and Department for Trade and Industry (2004) *Animal Welfare – Human Rights: Protecting people from animal rights extremists*, p7, available at: http://www.homeoffice.gov.uk/docs3/humanrights.pdf. In a parliamentary debate on 7 July 2004, the Parliamentary Under-Secretary of State for the Home Department, said 'Whatever the extremists say, most people in the United Kingdom – a recent survey gave the figure of 90 percent – believe that the use of animals for medical research is justified so long as it is done without causing unnecessary suffering to the animals'. See transcript, available at: 15) http://www.publications.parliament.uk/pa/cm200304/cmhansrd/vo040707/halltext/40707h02.htm. All accessed on: 7 Apr 2005.

16 See Chapter 1, footnote 14.

17 The study focused on attitudes towards genetic modification of animals and also considered the wider context of animal research. With regard to GM animals, views were similar; people had major concerns but generally accepted the use of the technology for medical research and testing. However, the group responded negatively to examples of genetic modification that would benefit humans in other ways, such as faster-growing farm animals and cats that do not cause allergies. Macnaghten P (2004) Animals in their nature: a case study on public attitudes to animals, genetic modification and 'nature' *Sociology* **38**: 533–51.

18 The Council published a Report on xenotransplantation in 1996. See Nuffield Council on Bioethics (1996) *Animal-to-Human Transplants: The ethics of xenotransplantation* (London: NCOB). Members of the Working Party on the ethics of research involving animals do not necessarily share the conclusions of other Council Reports.

regulatory context of research involving animals. In Chapter 3, we discuss the way in which moral philosophy relates to issues raised by such research. We focus in particular on the kind of questions that need to be asked when considering whether, and if so how, the use of animals by humans for research can be justified. We consider whether there are particular features of animals that are of special moral relevance, and we outline ways in which different philosophical frameworks can be related to morally relevant characteristics. We also discuss the relation of moral theory to regulatory codes and practices, and how it should contribute to achieving appropriate regulation. Chapter 4 explores philosophical and scientific issues in relation to the assessment of pain, suffering and distress caused by research on animals.

1.19 The areas of research in which animals are used are described in Chapters 5–9. They include: basic research to understand how animals and humans develop and function (Chapter 5), the use of animals for the study of human disease (Chapter 6), genetic modification of animals in the study of disease (Chapter 7), the development of medicines and vaccines by the pharmaceutical industry (Chapter 8) and toxicological testing of substances that are potentially hazardous for animals, humans or the environment (Chapter 9). Within each of these sections we provide examples of specific types of research. A summary of Chapters 5–9, that also considers in more detail the transferability to humans of results obtained from animal research, is provided in Chapter 10.

1.20 Chapters 11 and 12 discuss the Three Rs: Refinement, Reduction and Replacement. These terms represent widely accepted principles of humane experimental technique, whereby animals should be replaced by alternatives wherever possible, and the numbers and suffering of animals kept to a minimum. Chapter 11 focuses on replacements. It addresses the scope and limitation of the approach, and identifies scientific and non-scientific obstacles. Reduction and Refinement are similarly addressed in Chapter 12. An overview of the regulatory framework governing animal research in the UK and the formal provisions and operation in practice of the principal law, the Animals (Scientific Procedures) Act 1986 (A(SP)A), is provided in Chapter 13. Developments at the international level are also considered briefly.

1.21 The initial discussion of moral issues in Chapter 3 is resumed in Chapter 14. We aim to identify areas of practical consensus, which leads to some conclusions and recommendations for policy in Chapter 15. While our observations focus mainly on animal research in the UK, we have tried to consider the broader context and hope that the Report will be of use internationally.

1.22 As with all the Reports published by the Nuffield Council on Bioethics, this document has been produced primarily by a Working Party that was established for the specific purpose of writing this Report. The draft Report has also been considered, and commented upon, several times by all members of the Council, before final adoption. The members of the Working Party reflect in their own convictions the diversity of views held in the wider population. In the Report, we have avoided the search for a spurious show of agreement on all topics, but have instead attempted to clarify the varied ethical and scientific views that are held. Inevitably, some members of the group find some parts of the Report difficult to accept, and sometimes contrary to their own beliefs. It is therefore all the more important that a consensus statement was achieved after many hours of discussion (see paragraphs 15.3–15.20). Members have recognised that although disagreements will remain on both fundamental and very specific issues raised by animal research, nevertheless, all can respect the deeply held ethical convictions from which the views of others are derived.

1.23 It is in this spirit that we present this Report and its recommendations. Readers will therefore need to bear in mind that while the Working Party has tried scrupulously to give fair coverage to the widest possible range of ethical and scientific arguments, it is not possible, outside the consensus statement, to attribute to all members of the group the views described on any one issue. Rather, the Council adopted the Report as a whole, recognising it as a fair and balanced study of the wide range of views, trusting that it is valuable to lay out the range of opinions and beliefs about the use of animals in research, and to give a detailed analysis of the ethical arguments that should be the basis of any informed and fair debate.

# Chapter 2

## The context of animal research: past and present

# The context of animal research: past and present

## Introduction

2.1 This chapter concerns scientific, ethical and legal developments from a historical and contemporary perspective. We describe changes in public policy and public opinion and different forms of protests against animal research. We also consider the emergence of the concept of the Three Rs (Refinement, Reduction and Replacement; see Chapters 11 and 12), stakeholder and campaigning organisations, and animal-rights philosophy. We then briefly review the historical development and current provisions of the regulatory framework in the UK (see Chapter 13).

## Early forms of animal research in the biological and medical sciences

2.2 In some respects, the scientific and ethical reasons for using animals in scientific research have changed little from the first experiments in ancient Greece. Natural philosophers and physicians of those times wanted to increase their knowledge about the way in which complex organisms such as humans and animals functioned.[1] They valued the pursuit of knowledge for its own sake and sought to understand how and why the body malfunctioned, to learn about the development of disease and the effects of injury, and to discover better treatments and cures. Aware of biological similarities between humans and other animals, they hypothesised that many findings about specific mechanisms or processes in animals could be applied to humans.

2.3 Animal research continued to be undertaken in some societies over the next 2,000 years and formed part of the systematic scientific enquiry carried out in the Roman Era (c.510BC–455AD)[2] and in early Arabic medicine (from the fall of Rome until the 15th century).[3] There is little evidence of similar activity having taken place in medieval Europe. By the 16th century, methodological research had become more widespread, particularly in the medical schools of Italy. The Catholic Church forbade human autopsy, which could have contributed to biological and physiological knowledge and the effects of diseases. Instead, animals were used as the primary physiological and anatomical models.[4]

2.4 Most historians of medicine agree that many fundamental early discoveries in physiology were derived from studying animals. These discoveries include William Harvey's demonstration of blood circulation in 1628, Robert Hooke's discovery of the function of the lungs in 1667 and Stephen Hales' measurement of blood pressure in 1733.[5] This traditional view has been challenged by commentators who argue that animal research has led merely to increased knowledge about animals, but not necessarily about humans, thereby delaying

1 Rupke NA, Editor (1987) *Vivisection in Historical Perspective* (London and New York: Croon-Helm).

2 The notable physician Galen of the 2nd century AD, for example, argued that vivisection was the only way to reveal the function of biological structures. See Guerrini A (2004) Experimenting with Humans and Animals: From Galen to animal rights *JAMA* **291**: 2133–4; Orlans FB (1998) History and ethical regulation of animal experimentation: an international perspective, in *A Companion to Bioethics*, Kuhse H and Singer P (Editors) (Oxford: Blackwell).

3 For example, it is thought that the doctor and philosopher Al-Razi (or Rhazes) (864–930 AD) tested treatments on animals to evaluate their efficacy and side effects. See Bunch B and Hellemans A (Editors) (2004) *The History of Science and Technology* (Boston: Houghton Mifflin Company).

4 Hill RB and Anderson RE (1988) *The Autopsy – Medical Practice and Public Policy* (London: Butterworth).

5 Rhodes P (1985) *An Outline of the History of Medicine* (London: Butterworth).

progress in medical research.[6] They also contend, for example, that it has not been necessary for medical progress, claiming that clinical observations in humans had actually revealed these discoveries, which were then subsequently 'validated' in animals.[7] Thus, even if many fundamental discoveries did involve the use of animals, they argue that this practice should not be mistaken for evidence of the *necessity* of animal experiments.[8] Discussion about whether or not these assertions are justified, and what a world without previous and current animal research would be like, is interesting, but not straightforward. It involves a significant number of highly speculative and variable hypotheses. While we address some related issues in Chapter 3 (paragraphs 3.11–3.12), we consider it more fruitful to explore the current potential of Replacements (see Chapter 11) rather than to focus on what could have been achieved without animal research in the past.

### Box 2.1: Use of important terms

Throughout this Report, we make occasional reference to specific concepts and groups of people involved in the debate about animal research. We explain below how we use the terms to describe them. They should not be understood as rigidly defined categories, suggesting that people can only be grouped under one of the terms. We merely use them for practical reasons, to highlight particular points of view.

- **Defenders of research involving animals:** There are several organisations that have been set up by researchers or patients expressly to defend the use of animals in medical research on scientific and ethical grounds. Many other scientific and medical organisations publicly support the need to use animals in research (see Box 2.4).
- **Opponents of research involving animals:** This group includes those who believe that animal research is not scientifically and/or ethically justified and oppose its use.
- **Antivivisection groups:** Originally, this term was used to describe groups that opposed animal research that involved performing surgical procedures on living animals (vivisection literally means the 'cutting up' of a living being). It is now often used as a term to describe groups that oppose any experimentation on living animals, on either scientific or ethical grounds, or on both.
- **Animal rights:** A concept according to which most, if not all, animals are granted rights to live a life free from abuse and exploitation by humans. This would imply that animals must not be harmed for scientific purposes or any other purposes that benefit humans, other animals or the environment (see Box 3.4). This view is sometimes compatible with using animals in other contexts, for example as pets, provided that they are not treated merely as a means to an end. Those who espouse this principle differ in their views on how respect for animal rights should be promoted. Most restrict their actions to discussion in their immediate private environment; others campaign actively, but peacefully; a very small minority think it is justifiable to use unlawful, physical or psychologically violent actions with the aim of achieving an end to animal research or any other use they perceive as cruel.
- **Animal welfare:** This concept relates to the promotion and systematic study of all aspects of animal well-being. For animals involved in research, animal welfare includes the assessment of breeding, transport, housing, nutrition, disease prevention and treatment, handling and, where necessary, euthanasia. As a philosophical approach, the promotion of animal welfare is distinct from that of animal rights in the sense that those advocating respect for the welfare of animals do not necessarily wish to use the language of rights. Accordingly, animal-welfare groups emphasise human responsibility towards animals. They consider that some uses of animals may be acceptable (albeit with reluctance) provided they are adequately justified and carried out with full attention to the principle of the Three Rs, and that the behavioural and physiological needs of the animals concerned are addressed (see Box 2.4). Proponents of this approach are not necessarily committed to wishing an end to animal research, but most would see this state as desirable.
- **Animal protection groups:** An umbrella term for antivivisection, animal-rights and animal-welfare groups that seek to achieve the greatest possible protection of animals from inadequate treatment.

## Scientific developments and public opinion in the 18th and 19th centuries

2.5 As the study of animals developed in medical schools across Europe during the 17th and 18th centuries, experiments became increasingly complex and invasive. Due to the absence of anaesthetics, many experiments involved vivisection in the literal sense of the word (see Box 2.1), as some researchers frequently operated on unanaesthetised living animals as part of

6 See Europeans for Medical Advancement website at: http://www.curedisease.com/efma.htm. Accessed on: 8 Apr 2005; LaFollette H and Shanks N (1996) *Brute Science: Dilemmas of animal experimentation* (Routledge: London).

7 Greek CR and Greek JS (2000) *Sacred Cows and Golden Geese* (New York: Continuum), p19.

8 Greek CR and Greek JS (2000) *Sacred Cows and Golden Geese* (New York: Continuum), p16.

their research. This practice disturbed many of their contemporaries and concern about the suffering of experimental animals increased. There was also opposition to practices which involved the death of an animal simply to illustrate a previously known scientific concept: for example, in the 17th century, the physician Robert Boyle repeatedly demonstrated respiration to interested audiences by placing an animal in a bell jar, which was then depleted of air by a pump, causing the animal to suffocate.[9]

2.6 Concern was expressed in different ways. For example, Alexander Pope published the essay *Against Barbarity to Animals* in an English daily newspaper in 1713. William Hogarth's engravings, entitled *The Four Stages of Cruelty*, were published as inexpensive reprints in 1751 and enjoyed considerable popularity. Samuel Johnson denounced animal experiments in 1758 with a polemic published in the weekly news journal *The Idler*. While most contributions focused on animal suffering, there were also fears that lack of respect for animals would corrupt humans. Thus Thomas Percival expressed in *A Father's Instructions* in 1789: 'Cruelty…will steal your heart and every generous principle of your nature will be subverted'.[10]

2.7 During the 19th century there was a dramatic increase in scientific exploration in Britain and elsewhere. The study of evolution, and the natural sciences, often involved animal research. In France, a tradition of experimental physiology, involving large numbers of sentient animals, was initiated by Françoise Magendie (1783–1855) and his most famous pupil Claude Bernard (1813–78). In Germany in 1854, the visiting British journalist George Lewes observed 'extensive apparatus and no end of frogs'.[11]

2.8 Among other things, the substantial expansion of the middle classes in Victorian Britain, and increasing amounts of leisure time, contributed to growing concerns for animal suffering among lay people and scientists. Marshall Hall (1790–1857), a physician and noted physiologist, supported animal research but stated 'Unhappily… the subjects of animal physiology are sentient, and every experiment is attended by pain and suffering.'[12] Presaging later systems of regulation, Hall set out five guiding principles of animal research to stimulate debate in the scientific community:

i) the lack of an alternative;

ii) a clear objective;

iii) the avoidance of repetition of work;

iv) the need to minimise suffering; and

v) full and detailed publication of the results.[13]

2.9 In Britain, experimental physiology, which was the main form of medical research at that time, was relatively underdeveloped by comparison with the rest of Europe.[14] In 1863 an

9 See Thomas K (1996) *Man and the Natural World, Changing attitudes in England 1500–1800* (Oxford: Oxford University Press). See also a well-known painting by Joseph Wright from 1768 showing such an experiment being conducted, available at: http://www.nationalgallery.org.uk/cgi-bin/WebObjects.dll/CollectionPublisher.woa/wa/work?workNumber=NG725. Accessed on: 12 Apr 2005.

10 See also Shakespeare's *Cymbeline* Act 1, scene 5: 'your highness shall from this practice but make hard your heart'; Dunlop RH and Williams DJ (1996) Bioethics, animal experimentation and sentience, in *Veterinary Medicine: An illustrated history* (St. Louis, MO: Mosby), Chapter 32.

11 Wilson AN (2003) *The Victorians* (New York: W. W. Norton & Company).

12 In Dunlop RH and Williams DJ (1996) Bioethics, animal experimentation and sentience, in *Veterinary Medicine: An illustrated history* (Mosby), Chapter 32.

13 Rupke NA (Editor) (1987) *Vivisection in Historical Perspective* (London and New York: Croon-Helm).

14 Radford M (2001) *Animal Welfare Law in Britain: Regulation and responsibility* (Oxford: Oxford University Press), p67.

editorial in the leading medical journal, *The Lancet*, stated '… perhaps some two or three, or at most six, scientific men in London are known to be pursuing certain lines of investigation which require them occasionally during the course of a year to employ living animals for the purpose of their inquiries.'[15] However, in the mid-1860s, when general anaesthesia was introduced to Britain, a new generation of medical scientists began to experiment on animals rendered unconscious with ether or chloroform. According to government statistics, the number of animal experiments conducted in Britain increased from 250 in 1881 (the first year that records were kept) to 95,000 in 1910.[16]

2.10 Although there were sporadic examples of publications from the early 18th century onwards (see paragraph 2.6), formal public and political debate about animal research in Britain can be traced to the Annual Meeting of the British Medical Association (BMA) held in Norwich in 1874. The BMA had invited the French scientist Eugene Magnan to lecture on the physiological effects of alcohol. After the lecture, Dr Magnan gave a demonstration of the induction of experimental epilepsy in a dog by the intravenous injection of absinthe. There is no accurate record of what happened at the meeting, but it is known that some members of the audience protested and an eminent medical figure summoned the magistrates to prevent the demonstration from continuing. The Royal Society for the Prevention of Cruelty to Animals (RSPCA; see Box 2.4) brought a prosecution for cruelty, and several of the doctors present at the lecture gave evidence against Dr Magnan, who had returned to France to avoid answering the charges. The press followed these events with interest, and a heated debate unfolded in the pages of popular magazines. The very first animal protection pamphlets, calling for legislation to regulate animal research, appeared shortly after the BMA meeting.[17]

2.11 Over the next two years, the debate gathered momentum. The first animal protection society was formed in 1875 by the writer and suffragette Frances Power Cobbe.[18] She had returned from Italy earlier that year, having organised a campaign against the use of dogs and other animals in experiments conducted by an Italian professor of physiology. She also founded the British Union for the Abolition of Vivisection in 1898, based on the principle of total abolition (see Box 2.4).[19] In 1875 Cobbe helped to introduce a bill into Parliament that called for the regulation of animal experiments.

2.12 The medical and scientific professions responded to what they had not previously perceived to be a serious threat to biological and medical research by countering the bill with a second, less restrictive draft. In an attempt to resolve the issue, a Royal Commission was established. It recommended in January 1876 that the practice of animal research should be regulated by law. In view of the two proposals, new legislation was prepared and introduced into the House of Lords in May of that year. The General Medical Council collected 3,000 signatures calling for amendments and a revised Bill was finally accepted by the Government, becoming the 1876 Cruelty to Animals Act.[20] This was the first legislation in the world to regulate

15 Anon (1863) *The Lancet* ii: 252–3.

16 French RD (1975) *Antivivisection and Medical Science in Victorian Society* (Princeton: Princeton University Press).

17 Hopley E (1998) *Campaigning Against Cruelty – The hundred year history of the British Union for the Abolition of Vivisection* (London: BUAV), p4; French RD (1975) *Antivivisection and Medical Science in Victorian Society* (Princeton: Princeton University Press).

18 The *Society for the Protection of Animals Liable to Vivisection* later became the *Victoria Street Society* and then the *National Anti-Vivisection Society* (see Box 2.4).

19 Hopley E (1998) *Campaigning against Cruelty – The hundred year history of the British Union for the Abolition of Vivisection* (London: BUAV).

20 French RD (1975) *Antivivisection and Medical Science in Victorian Society* (Princeton: Princeton University Press); Hopley E (1998) *Campaigning against Cruelty – The hundred year history of the British Union for the Abolition of Vivisection* (London: BUAV), p5; Radford M (2001) *Animal Welfare Law in Britain: Regulation and responsibility* (Oxford: Oxford University Press), p67.

animal research. The 1876 Act allowed certain experiments, but required that licence applications be reviewed and authorised. Decisions about licences were taken by the Secretary of State, but required eminent supporters, usually Presidents of the Royal Medical Colleges. Licences were administered by the Home Office (see paragraphs 13.2–13.3).

2.13 Between 1876 and the start of the First World War, public debate about animal research flourished in the UK, with the founding of several animal protection organisations and the establishment of a second Royal Commission in 1906.[21] Several public lectures took place, and a great number of books and leaflets addressing concerns about animal research were published.[22]

## Developments in policy and public opinion

### *The principle of humane experimental technique: the Three Rs*

2.14 Throughout the first half of the 20th century, the use of animals in biological and medical research increased greatly under the regulatory licensing system, despite continuing protests. Although active opposition to animal research was at a relatively low level between the 1920s and 1960s, changes in the way animals were treated, and increased understanding of the capacity of animals to suffer pain and distress led to the first radical scientific reassessment of the 1876 Act.

2.15 Two pioneers of laboratory animal welfare were the UK scientists Professor William Russell and Rex Burch. In 1958, the Universities Federation for Animal Welfare (UFAW), an organisation committed to advancing animal welfare in research through support for studies on humane techniques (see Box 2.3), awarded fellowships to Russell and Burch to study ethical aspects of animal research. Their seminal book, *The Principles of Humane Experimental Technique*, published the following year, defined the principle of the Three Rs (Refinement, Reduction and Replacement of animal experiments) as the basis for more humane experimental practices (see Box 2.2). The concept initially attracted little attention. It was not until 1978 when Professor David Smythe (then Chairman of the Research Defence Society, RDS; see Box 2.4) published the book *Alternatives to Animal Experiments*, that scientists started to become more aware of

#### Box 2.2: The Three Rs

The Three Rs are discussed in more detail in Chapters 11 and 12. We reproduce here the definitions as presented by Russell and Burch in 1959:*

**Refinement:** Any decrease in the incidence of severity of inhumane procedures applied to those animals which are used.

**Reduction:** The reduction in the number of animals used to obtain information of given amount and precision.

**Replacement:** The substitution of conscious living higher animals with insentient material.

* See Russell WMS and Burch RL (1959) *The Principles of Humane Experimental Technique* (London: Methuen & Co. Ltd.), available at: http://altweb.jhsph.edu/publications/ humane_exp/het-toc.htm. Accessed on: 15 Apr 2005.

21 The Commission was established in response to renewed public concern about animal research that had arisen, at least partly, from a trial of Stephen Coleridge, Secretary of the National Anti-Vivisection Society (see Box 2.4). In 1903, he had quoted from the book *The Shambles of Science* at a public meeting. The book was published by two antivivisectionists and described their experiences as medical students in London. Coleridge was successfully sued for defamation by a scientist, but the evidence revealed at the trial and the subsequent popularity of the book from which Coleridge had quoted led to an increase in sensitivity about animal research. A statue of a small brown dog was subsequently erected in Battersea Park, London in 1906. The inscription read: 'In memory of the brown terrier dog done to death in the laboratories of University College in February 1903 after having endured vivisection extending over more than two months and having been handed over from one vivisector to another till death came to his release. Also in memory of the 232 dogs vivisected in the same place during the year 1902. Men and women of England: How long shall these things be?' The statue became the symbol of the controversy surrounding vivisection and attracted a series of demonstrations and counter demonstrations. In 1907, some hundred medical students tried to destroy the statue, but were prevented by local residents and the police. Considering the controversy afresh from first principles, the Commission concurred with the findings of the first Commission and saw no need for any major revisions to the statutory framework. A number of administrative changes were suggested, such as an increase in staff of the inspectorate and refinement of methods of handling animals. See Radford M (2001) *Animal Welfare Law in Britain: Regulation and responsibility* (Oxford: Oxford University Press), p71–2.

22 See Hopley E (1998) *Campaigning against Cruelty – The hundred year history of the British Union for the Abolition of Vivisection* (London: BUAV).

the Three Rs. Since the mid-1980s, knowledge about the concept has increased among scientists, and it has since been accepted in many parts of the world. While many stakeholders would argue that each of the Three Rs is equally important, there are also organisations dedicated specifically to the Replacement approach (see Box 2.4 and Chapter 11).

### Box 2.3: Humane research trusts

***Dr Hadwen Trust***

http://www.drhadwentrust.org.uk

Established in 1970, the Dr Hadwen Trust is a medical research charity that funds the development of alternatives to replace animal experiments in biomedical research and testing. The Trust aims to contribute to the replacement of animals while furthering research into major health problems such as cancer, heart disease, meningitis and Alzheimer's disease. Researchers sponsored by the Trust do not conduct research on animals or animal tissues.

***Humane Research Trust***

http://www.humaneresearch.org.uk

The Humane Research Trust is a fund-raising charity supporting medical research into human disease without the use of animals or animal tissue. It aims to eliminate the need for animals in the medical sciences. Established in the late 1960s the Trust works with scientists, funding a wide range of projects at UK hospitals and universities. The Trust also funds lectureships and studentships and hosts scientific conferences.

2.16 In the latter half of the 20th century, the study of animal welfare and animal behaviour became increasingly established as scientific disciplines. A number of animal-welfare organisations, especially the UFAW, the Fund for the Replacement of Animals in Medical Experiments (FRAME) and the RSPCA (see Box 2.4), contributed to this development. They established working relationships with organisations emerging within the scientific community which had a specific interest in laboratory animal welfare including the Laboratory Animals Science Association (LASA), the Institute of Animal Technology (IAT) and the Laboratory Animal Veterinary Association (LAVA; see Box 2.4). All of these groups contributed to the developing legislation. In the European Union (EU), the establishment of the European Centre for the Validation of Alternative Methods (ECVAM; see Box 2.4) was a significant step towards achieving the promotion of the Three Rs across Member States.

### Box 2.4: Campaigning and stakeholder organisations focusing on scientific and ethical issues raised by animal research

#### Animal-welfare organisations

***Universities Federation for Animal Welfare (UFAW)***

http://www.ufaw.org.uk

UFAW is an independent animal-welfare organisation that was founded in 1926 by Major Charles Hume, based on his belief that 'animal problems must be tackled on a scientific basis, with a maximum of sympathy but a minimum of sentimentality'. UFAW has since played a major role in improving conditions for animals. The organisation focuses on promoting scientific knowledge and expertise to improve the welfare of pets, zoo animals and laboratory animals, as well as in agriculture. UFAW funds research, holds symposia, gives advice to the Government and others, and produces publications on animal welfare, including the journal *Animal Welfare* and the *UFAW Handbook on the Care and Management of Laboratory Animals*.

***Fund for the Replacement of Animals in Medical Experiments (FRAME)***

http://www.frame.org.uk

FRAME was founded in 1969 to promote the Three Rs and to raise awareness about alternative methods. FRAME also publishes the peer-reviewed scientific journal *ATLA* (*Alternatives to Laboratory Animals*). The Fund takes the view that the current scale of animal research is unacceptable, while recognising that immediate abolition of all animal experiments is not a feasible option. Its long-term aim is to replace the use of laboratory animals through the development, validation and acceptance of alternative methods. In1983, FRAME joined with the British Veterinary Association (BVA) and the Committee for the Reform of Animal Experimentation (CRAE) to advise the Government on what would become the Animals (Scientific Procedures) Act 1986 (A(SP)A). In 1991, the FRAME Alternatives Laboratory (FAL) was opened at the University of Nottingham Medical School.

***Royal Society for the Prevention of Cruelty to Animals (RSPCA)***

http://www.rspca.org.uk

The RSPCA was established in 1824 as the first national animal protection society in the world. The Society is involved in preventing cruelty and promoting animal welfare in a wide range of uses of animals, as well as being an active campaigning organisation. It employs veterinary and scientific experts to identify animal-welfare concerns, and to devise ways of resolving them for farm livestock, wildlife, pets and animals used in research. The Society is opposed to all animal experiments that cause pain, suffering, distress or lasting harm. It believes that the benefit and justification for animal use should be challenged on a case by case basis, and promotes the development and implementation of the Three Rs.

Since the early 20th century, the RSPCA has taken an active role in ensuring the sound application of legislation that protects animals. Upon receiving royal approval in 1840, an inspector was appointed to ascertain the treatment of animals in markets and slaughterhouses. Today, the Society comprises a national network of 187 branches, several animal hospitals, an emergency service for injured, trapped or stranded animals, and a national cruelty and advice telephone line.

The RSPCA has been influential in shaping UK legislation on animal welfare and also places emphasis on educating students, teachers, youth organisations and trainers about animal welfare. A range of National Curriculum resources is available, and activity days and courses are held at four education centres. In 1980, the RSPCA established the Eurogroup for Animal Welfare, the first coalition of animal-welfare groups in Europe.

## Professional bodies focusing on improving standards in laboratory animal science, care and welfare

***Laboratory Animals Science Association (LASA)***

http://www.lasa.co.uk

The UK LASA was founded in 1963 by representatives from industry, academia, government and the research councils. Their aim was to establish an organisation which provided information and a forum for ideas on the science of using animals in research.

LASA provides advice to its members in the scientific community on developments in the Three Rs, good practice and techniques. LASA acknowledges the relevance of ethical issues raised by animal research and constantly reviews its policies. The Association also addresses ethical issues in its training courses. LASA is a member of both the Federation of European Animal Science Associations (FELASA) and the International Council for Laboratory Animal Science (ICLAS).

***Laboratory Animal Veterinary Association (LAVA)***

http://www.lavavet.org

A division of the British Veterinary Association, LAVA focuses on veterinary care and all aspects of the welfare of laboratory animals. LAVA's members are veterinary surgeons involved in a wide range of laboratory-based animal medicine and science. Many members act as Named Veterinary Surgeons under the A(SP)A. LAVA is active in training and keeping members abreast of recent developments in the promotion of laboratory animal welfare.

***Institute of Animal Technology (IAT)***

http://www.iat.org.uk

The Animal Technicians Association, the IAT's predecessor, was established in 1950. The IAT aims to advance and promote excellence in the care and welfare of animals in science, recognising that while humans have a moral and legal obligation to care for each other by prolonging life and alleviating suffering, there is also an obligation to ensure that the animals used to further these aims are properly cared for and protected.

The Institute has developed training courses for animal technicians, produced publications and introduced qualifications. In 1985, a Register of Animal Technicians was established to emphasise the Institute's position on the ethical and legal aspects of care of laboratory animals. Many members of the Register, who are bound by a code of ethics, are specified as Named Animal Care and Welfare Officers (NACWO) under the A(SP)A and are responsible for the care of animals in designated establishments.

## European Centre for the Validation of Alternative Methods (ECVAM)

http://ecvam.jrc.cec.eu.int

ECVAM was established by the European Commission in 1992 to actively support the development, validation and acceptance of methods that could reduce, refine or replace the use of laboratory animals, implementing the provisions of Directive EEC 86/609. Its main activities are:

- to coordinate the validation of alternative test methods in the EU;
- to act as a focal point for the exchange of information on the development of alternative test methods;
- to set up, maintain and manage a database on alternative procedures; and
- to promote dialogue between legislators, industry, biomedical scientists, consumer organisations and animal-welfare groups, with a view to the development, validation and international recognition of alternative test methods (see paragraph 11.34).

In the UK, a National Centre for the Three Rs (NC3Rs) was established in 2004 (see box 11.3).

## Organisations defending the use of animals in research

***RDS Understanding Animal Research in Medicine (formerly the Research Defence Society)***

http://www.rds-online.org.uk

Founded in 1908, the RDS is a UK-based organisation representing medical researchers in the public debate about the use of animals in medical research and testing.

RDS provides a public information service about the role of animal research, the controls under which research is carried out and the benefits that have resulted. It also liaises with the media and Members of Parliament, providing information, briefings, talks, interviews and arranging visits to research laboratories. RDS is funded by its members, most of whom are medical researchers, doctors and veterinary surgeons. Corporate members include research institutes, university departments, medical research charities, learned societies and pharmaceutical companies.

***Association of the British Pharmaceutical Industry (ABPI)***

http://www.abpi.org.uk

The ABPI is the UK pharmaceutical industry's pre-eminent association, representing about 100 companies that produce prescription medicines. Its member companies research, develop, manufacture and supply more than 90 percent of the medicines prescribed through the National Health Service (NHS) and are major exporters to other countries. Contract research organisations and other companies that support the pharmaceutical industry are affiliate members.

Under the auspices of its Research and Development Committee, the ABPI's Animal Research and Welfare Advisory Group plays an active role in promoting best practice in animal welfare and implementing the Three Rs. The ABPI also supports science education from primary through to university level, producing educational materials that describe critical areas of science and technology, and explain the role of the pharmaceutical industry in the development of new medicines, the use of animals in research and the regulatory context.

***Association of Medical Research Charities (AMRC)***

http://www.amrc.org.uk

The AMRC is a membership organisation of over 100 UK charities that fund medical and health research. It was founded in 1972 and established as a charity in 1987.

The AMRC aims to provide support and leadership for its members and the wider charity sector involved in medical and healthcare research through the provision of information and guidance. Member charities are obliged to use peer-review processes in allocating funding, and they are required to support, among other things, AMRC position statements on the use of animals in medical research. AMRC members are committed to ensuring that they support the most effective research in the right environment and that the researchers they fund follow good-practice guidelines in their work.

***Coalition for Medical Progress (CMP)***

http://www.medicalprogress.org

The CMP is an alliance of organisations that share the common aim of seeking to ensure that the UK continues to lead advances in human and animal medicine. Researchers, funding bodies such as the Medical Research Council (MRC) and the Wellcome Trust and professional bodies including IAT, LASA, LAVA (see above) cooperate in this initiative to explain and illustrate the need for research involving animals and its benefits, and to respond to specific issues of public interest.

## Anti-vivisection organisations

***National Anti-Vivisection Society (NAVS)***

http://www.navs.org

Established in 1875 as the Victoria Street Society, the NAVS was the world's first organisation campaigning against animal experiments. The Society was founded by the humanitarian Francis Power Cobbe, who in 1898 left to form the BUAV.

The NAVS operates through public education, political lobbying and publicity campaigns, and produces technical reports, educational literature, books and films. The Society funds non-animal research through the Lord Dowding Fund for Humane Research, a department of the NAVS. In 1990, NAVS founded Animal Defenders International, to campaign on a broader range of animal and environmental issues.

***British Union for the Abolition of Vivisection (BUAV)***

http://www.buav.org

Founded in 1898, the BUAV opposes all animal experiments on both ethical and scientific grounds. The organisation is dedicated to ending animal experiments, both nationally and internationally, through public campaigning, undercover investigations, media activities, political lobbying, corporate relationships, the provision of legal and scientific expertise, and the production and distribution of educational and information materials. Campaigns cover issues such as the use of animals in the testing of cosmetics, household products, chemicals and pet food, their use in medical research and the genetic modification of animals.

The BUAV coordinates the European Coalition to End Animal Experiments (ECEAE) and is a founder member of the International Council for Animal Protection in OECD Programmes (ICAPO).

***The emergence of animal-rights philosophy***

2.17 From the 1970s onwards, ethical issues raised by animal research received increasing attention in academic discussion, and a number of influential contributions were made to the debate. In 1975, Dr Richard Ryder published the influential book, *Victims of Science*, and coined the term 'speciesism' to liken the treatment of animals by humans to forms of unjustified discrimination, such as racism or sexism (see Box 3.4).[23] In the same year, another influential book was published, *Animal Liberation*, written by the Australian philosopher Professor Peter Singer. Singer argued that the suffering of most animals should be given equal consideration to the suffering of most humans. The book is regarded by many of those opposed to animal research as the manifesto for their movement, and provides the ethical rationale for the activities of a number of campaigning groups. However, we note that Singer argued from a utilitarian perspective (see paragraphs 3.52–3.55), which is not accepted by all of those opposed to animal research. Moreover, the concept of ascribing 'rights' to animals is usually not associated with utilitarian approaches. A significant contribution setting out a rights-based approach was made in 1983 by Professor Tom Regan in *The Case for Animal Rights*.

2.18 While some animal protection groups stimulated debate through academic discussion, books and leaflets, others sought to influence policy makers more directly. In 1977, the Committee for the Reform of Animal Experimentation (CRAE) was founded and began lobbying government for new legislation on animal research.

***Undercover investigations/infiltrations undertaken by animal protection organisations***

2.19 The two main anti-vivisection societies in the UK are the BUAV and the NAVS (see Box 2.4). They believe that animal research often takes place in secret and therefore they seek to draw attention to the issue by conducting undercover investigations of animal facilities. They aim to demonstrate to the public the severity of licensed research involving animals and have made numerous allegations of unlawful practices in some cases (see Box 2.5).[24]

23 Ryder R (1975/1983) *Victims of Science: The Use of Animals in Research* (London: Open Gate Press).

24 See, for example, the BUAV website *Exposing secrets*, available at: http://www.buav.org/undercover/secrets.html. Accessed on: 11 Mar 2005.

## Box 2.5: Examples of undercover investigations /infiltrations

- In 1975 the *Sunday People* newspaper published an exposé of 'smoking beagles' at laboratories belonging to Imperial Chemical Industries (ICI), which aroused wide public interest. The article carried explicit pictures of dogs that were confined to small boxes and forced to inhale tobacco smoke through devices attached to their muzzles. The research had the aim of testing the efficacy of tobacco substitutes, but adverse publicity resulted in its termination.
- In 1989–90 an undercover investigator recorded video- and audio-tape material and took photographs of experiments involving cats and rabbits conducted by Professor Wilhelm Feldberg and his assistant at the MRC's National Institute for Medical Research (NIMR) at Mill Hill in London. The professor was conducting basic research on the effects on blood sugar of heating the abdomen of an animal. Following the investigation, the 89-year-old scientist was accused of inadequately anaesthetising animals, poor performance and leaving anaesthetised animals unattended. The two researchers returned their licences to the Home Office before an inquiry into the matter was established by the MRC (there was some confusion in the reports at the time as to whether the licences were to be revoked or whether this was a voluntary measure). The inquiry found that, as a result of a failure by the researchers to maintain anaesthesia of sufficient depth, up to four rabbits experienced avoidable suffering. The inquiry also found that the Director of the NIMR (as the certificate holder) and the Named Veterinary Surgeon had failed in their statutory duties under the A(SP)A. As a result the Home Office required the Director to implement a number of changes at the Institute. In addition, the Home Secretary decided that nobody over the age of 70 should hold a project licence.*
- In 1989, a BUAV undercover investigator joined the contract research organisation (CRO)[25] Huntingdon Research Centre, now Huntingdon Life Sciences (HLS), as a weekend cleaner of the rodent and dog facilities. She produced photographic images, some of which were published together with a report in the British newspaper *Today*, and subsequently in publications of the BUAV. The report accused HLS of condoning unnecessary animal suffering and providing poor housing conditions. The subsequent investigation by the Home Office concluded that the company had not committed any legal offence.† HLS was infiltrated again in 1996 by an investigative journalist. The investigator filmed amongst other things a member of staff punching a beagle that was being held by a colleague, and the footage was included in a television programme. The two employees were subsequently prosecuted under the Protection of Animals Act of 1911 and admitted to charges of 'cruelly terrifying dogs'. They were given community service orders and were dismissed from their employment.‡
- Wickham Research Laboratories, a CRO, was the subject of an undercover investigation by the BUAV in 1993. The investigator reported breaches in Home Office licence conditions and inadequate animal housing facilities. It was also alleged that the Home Office was sanctioning procedures for which non-animal methods were available. The Home Office Inspectorate and the Medicines Control Agency investigated these allegations. Their report disclosed poor management which had led to lax attitudes and practices among certain members of staff including the falsifying of test and environmental data. One case of unnecessary use of animals was also identified and some aspects of staff training were declared 'unsatisfactory'. Responsibility for these failures was found to lie with the line manager for the named 'day-to-day care person' at the time. It was recommended that the manager, who had subsequently become the 'day-to-day care person' by the time of the Home Office investigation, should be replaced and his personal licence revoked. A number of other members of staff at Wickham received letters of admonition. The company was also directed by the Home Office to agree to a formal training scheme for all staff in its animal unit and to revise standard operating procedures. However, the Junior Minister of the Home Office, who reported the findings, said that he was satisfied that all the work at Wickham was properly licensed under the A(SP)A and that some of the other principal allegations above were also not substantiated.∫
- The NAVS undertook an undercover investigation at the Charing Cross and Westminster Medical School in 1994–5. Members of the Society reported the killing of rodents that were surplus to requirements and which had not been used, and improper killing methods. The organisation presented its report on the matter, Access Denied, to the Home Office and the Animal Procedures Committee. In 1996 the Home Office Inspectorate carried out an investigation into the allegations. The Inspectorate identified 'irregularities in the application of approved methods for the humane killing of animals and deficiencies in middle management'. The certificate of designation (see paragraph 13.8) was revoked and a new certificate was issued once the medical school had met certain criteria set by the Home Office. These included the retraining of staff, the putting in place of operating procedures and changes to the animal care arrangements.**
- A BUAV infiltration took place at a primate research facility at Cambridge University in 2001–2. The BUAV alleged unprofessional care of animals involved in procedures, supported by video documentation. The Home Office was asked to review whether the circumstances of the research were acceptable under the terms of the project licence. The subsequent review by the Home Office concluded that the severity limits and bands for the projects, none of which was classed as higher than 'moderate', were correctly assigned, and that there was no evidence for the BUAV's main allegations. However, having scrutinised details of all procedures performed extending back to 1998, four instances of non-compliance with licence authorities were identified by the Chief Inspector's review. In 2004–5 the BUAV sought a judicial review against the Home Office on specific points relating to both the A(SP)A licences and the care of the monkeys they had filmed at Cambridge. The BUAV have been granted

25 Contract research organisations (CROs) usually conduct specific research on behalf of companies or institutes which, for logistical or other reasons, do not undertake the research themselves. In some cases, this research involves the safety testing of new medicines and other products including household chemicals and agrochemicals.

permission to proceed on two of the grounds relating to the former. The other grounds have not been allowed to proceed, although at the time of writing the BUAV is considering appealing against this decision.††

- In 2003 the BUAV reported its findings of an undercover investigation undertaken in Germany within Covance, a CRO. The BUAV alleged that Covance had breached German animal-welfare legislation. Covance denied the allegations and an investigation was initiated by the German authorities. All accusations were found to be groundless. In July 2004, the BUAV submitted a complaint to the European Commission stating that the German authorities had failed to properly transpose into national law the EU Directive regulating animal experiments. The BUAV also asserted that appropriate sanctions against Covance for breaches of German animal-welfare law had not been imposed. In refusing Covance's application for an injunction, the appeal court in Nordrhein Westfalen allowed the dissemination of video and photograph material obtained by the investigator.‡‡

* The investigator subsequently wrote a book detailing her experiences. MacDonald M (1994) *Caught in the Act: The Feldberg Investigation* (Jon Carpenter Publishing). See Coghlan A (1990) MRC launches inquiry into animal experiments *New Scientist* **1720** 9 June; Ward L (1992) Time for talk across the trenches: The two sides in the antivivisection debate must stop sniping at each other if they are ever to find some common ground *New Scientist* **1820** 9 May; Hampson J (1992) The secret world of animal experiments: Despite the 1986 act, the public still has little say on what is done in animal experiments. Ethical committees could give lay people a voice *New Scientist* **1816** 11 April. See also *Written Answers to Questions*, House of Commons debate (1991), available at: http://www.publications.parliament.uk/pa/cm199091/cmhansrd/1991-03-11/Writtens-1.html. Accessed on: 14 Apr 2005; NAVS (1996) *Access Denied Legal Critique*, available at: http://www.navs.org.uk/download_files/publications/reports/Access_Denied1Legal_Critique.pdf. Accessed on: 14 Apr 2005; Animal Procedures Committee (1991) *Report of the Animal Procedures Committee for 1990* (London: HMSO), available at: http://www.apc.gov.uk/reference/ar90.pdf. Accessed on: 22 Apr 2005.

† See BUAV report of the infiltration, BUAV *Huntingdon Life Sciences*, available at: http://www.buav.org/undercover/hls.html. Accessed on: 11 Mar 2005.

‡ The television programme referred to was the 1997 Channel 4 documentary *It's a Dog's Life*; see also an article by the undercover investigator, Broughton A (2000) Seeing is Believing: Animals rights abuse exposed *The Ecologist* 22 February, available at: http://www.theecologist.org/archive_article.html?article=203&category=59. Accessed on: 11 Mar 2005.

∫ BUAV *Wickham Research Laboratories*, available at: http://www.buav.org/undercover/wickham.html Accessed on: 23 Feb 2005; House of Commons debate (1993), available at: http://www.parliament.the-stationery-office.co.uk/pa/cm199293/cmhansrd/1993-06-22/Writtens-1.html. Accessed on: 23 Feb 2005.

** NAVS *Charing Cross and Westminster Medical School NAVS undercover investigation 1994-95*, available at: http://www.navs.org.uk/vivisection/inside/cc_westminster.htm; See also House of Commons (1997) *Written Answers to Questions*, available at: http://www.parliament.the-stationery-office.co.uk/pa/cm199798/cmhansrd/vo970730/text/70730w01.htm. Accessed on: 22 Feb 2005.

†† See BUAV website for details of the initial investigation, a response to the Home Office's review and press release, available at: http://www.buav.org/undercover/cambridge.html and http://www.buav.org/news/2005/02-04.html; (2002) *Aspects of Non-human Primate Research at Cambridge University: A Review by the Chief Inspector*, available at: http://www.homeoffice.gov.uk/docs/cambridge.html; University of Cambridge (2003) *Statement on Home Office Report*, available at: http://www.admin.cam.ac.uk/news/press/dpp/2003021101. All accessed on: 14 Apr 2005; BUAV (2005) Press Release *Judicial review investigating cruelty to monkeys at Cambridge University set to proceed*, available at: http://www.buav.org/press/2005/0412.html. Accessed on: 22 Apr 2005; RDS (2005) *Antivivisectionists' legal challenge - the facts*, available at: http://www.rds-online.org.uk/pages/news.asp?i_ToolbarID=6&i_PageID=1816. Accessed on: 22 Apr 2005.

‡‡ BUAV *Poisoning for Profit*, available at: http://www.buav.org/covance/index.html. Accessed on: 14 Apr 2005; European Biomedical Research Association Winter Bulletin (2003) *Infiltration of Covance in Germany*, available at: http://www.ebra.org/bulletin/win05_03.html. Accessed on: 14 Apr 2005; BUAV (2004) Press release *Covance: BUAV makes official complaint to EU Commission*, available at: http://www.buav.org/news/2004/07-15.html. Accessed on: 14 Apr 2005; Court of Appeal Nordrhein Westfalen (2004) Press release *Bilder aus Tierversuchslabor dürfen teilweise veröffentlicht werden* (Aktenzeichen 3 U 77/04), available at: http://www.olg-hamm.nrw.de/presse/archiv/2004/tiervers.htm. Accessed on: 22 Apr 2005.

2.20 Opponents of undercover investigations view them as unlawful and possibly illegal infiltrations.[26] They argue that the investigators provide untruthful information when applying for jobs and at interviews, and that they act unlawfully during their time at the institution, for example by disclosing confidential information. They also argue that many infiltrations fail to produce any compromising evidence, and that these findings are not published. Where findings are published, critics assert that reports are often highly selective in the facts that are presented and that they therefore do not do justice to the claim of showing the reality of animal research. Many establishments also have 'whistleblowing' procedures in place, that require staff to report breaches of codes of conduct to supervisors, facility managers or to the

26 Some opponents prefer to describe infiltrations as illegal, rather than unlawful, suggesting breaches of the criminal rather than the civil law. However, most activities associated with infiltration, such as the publication of confidential data, which is usually not compatible with contracts of employment, breach the civil law. The criminal law can be invoked in cases where employment is obtained by deception (Theft Act 1968 s.16(2)(c)), or in cases where material is removed from laboratories (Theft Act 1968 s.1). An important criterion in deciding about the applicability of these offences is 'dishonesty', which is a relatively vague concept relating to whether or not the action was contrary to accepted standards in society.

Certificate Holder. Opponents of infiltrations argue that those concerned about animal welfare should use these procedures, instead of publishing reports. According to this view, infiltrations are unacceptable, and prevent the building of trust between researchers and animal protection organisations. Infiltrations are thought to obstruct the pursuit of an open and factual discussion about animal research.

2.21 Proponents of undercover investigations, on the other hand, assert that research is being conducted in secrecy and that insufficient information, particularly about the suffering of animals involved in research, is available. They take the view that publication of undercover investigations is in the public interest as it can help to demonstrate the reality of animal research and to expose cases of malpractice, abuse of animals and poor scientific practice. Proponents believe that investigators join research institutes legally, and that their reports should therefore be viewed as legitimate records of practices that are kept secret from the public and Parliament.

***Organised unlawful protests against animal research since the 1970s***

2.22 A very small fraction of those opposing research involving animals employ unlawful or extreme means of protest. They adopt violent or intimidating action towards researchers and their families, and also against those who are associated with organisations conducting such research, for example customers, shareholders, suppliers and other customers of suppliers.

2.23 Criminal activities began in the UK with arson attacks on pharmaceutical laboratories in the 1970s. During this decade, the Animal Liberation Front (ALF) was formed in the UK, and started a campaign of 'freeing' or 'liberating'[27] animals from laboratories, causing unlawful damage in the process. Their tactics became increasingly violent, and in 1982 the ALF sent letter bombs to the leaders of the four main political parties in the UK, injuring a civil servant.[28] In 1985, petrol-bomb attacks on the homes of a small number of medical researchers were carried out. Later that year, the Animal Rights Militia claimed responsibility for two bombs planted under the cars of scientists. During the next ten years, protesters frequently targeted researchers whose work involved animals, as well as company sites linked with research or food testing.[29]

2.24 In the 1990s, a campaign against the CRO HLS was launched. Staff of the company, as well its shareholders, banks, stockbrokers and clients, were harassed in different ways and many employees received hate mail and death threats, or had damage caused to their houses and cars. Senior staff of HLS were attacked physically, and on a few occasions hoax bombs were sent.[30] A group of animal-rights activists launched an initiative under the name Stop Huntingdon Animal Cruelty (SHAC). Although SHAC states on its website that it does not encourage illegal activities, some of its leading members have been convicted of criminal offences.[31] The protests have led some companies to withdraw their financial and auditing services from HLS, including its major creditors, the Royal Bank of Scotland. The UK Government, which also supported the company during the early phases of SHAC's protest, has agreed to provide banking and insurance facilities for the company.[32] Protestors have

27 In many cases, animals that are taken from laboratories and placed in their natural environment subsequently die because they are insufficiently adapted to the new environment. In some cases where farmed mink have been released into the British countryside there was a subsequent marked decline in the numbers of native voles. Hence, there has been debate as to whether the act of 'freeing' the animals is beneficial. Some organisations assert that they have placed liberated animals in good homes.

28 Henshaw D (1989) *Animal Warfare* (London: Fontana Press).

29 Matfield M (1996) The animal liberation front: terrorist attacks on animal research *Scand J Lab Anim Sci* **23**: 31–5.

30 For victims' accounts see the Victims of Animal Rights Extremism website, available at: http://www.vare.org.uk/vctms.html Accessed on: 14 Apr 2005.

31 See Huntingdon v SHAC judgement (2004) Neutral Citation Number EWHC 1231 (QB), available at: http://www.bailii.org/cgi-bin/markup.cgi?doc=/ew/cases/EWHC/QB/2004/1231.html&query=1231&method=all. Accessed on 11 Mar 2005.

32 Clark A (2001) Bank of last resort *The Guardian* July 2, available at: http://education.guardian.co.uk/businessofresearch/story/0,9860,515646,00.html. Accessed on: 14 Apr 2005.

also mounted a continuing campaign against the owners of a facility for guinea pigs used in research, based in Staffordshire. Some of these protests are lawful, although there have also been a number of unlawful activities carried out by unidentified campaigners. These include desecration of the grave and stealing of the body of a relation of the Hall family, who operate the breeding facility, in October 2004.[33] We return to the issue of animal-rights-related violence and its implications in Chapters 14 and 15 (Chapters 14 and 15 (paragraphs 14.63 and 15.47–15.50).

### *The origins of the UK Animal (Scientific Procedures) Act 1986*

2.25 In the early 1970s, the Council of Europe set up an *ad hoc* committee of experts to draft a convention to establish guidance for animal research. This body developed a framework for legislation and guidelines for laboratory animal housing, which was transposed with very few additions into Directive EEC 86/609 of the European Economic Community (the predecessor of the EU) in 1985. The Directive required Member States to adopt national legislation, or similar controls, on animal research in the light of its provisions (see paragraph 13.3).[34]

2.26 Meanwhile, pressure for new legislation had been growing in the UK.[35] The combination of the impending Directive EEC 86/609 and the willingness of the Home Office Minister at the time to respond to concerns about the age of the 1876 Act led to the drafting of a bill in 1985. CRAE formed an alliance with the BVA and the scientific charity FRAME (see Box 2.4). Working together, these organisations had a strong influence on the drafting of the Animals (Scientific Procedures) Act (A(SP)A), which was passed in 1986.[36] The cornerstone of the Act, which is described in more detail in Chapter 13, is the cost-benefit assessment,[37] which focuses on an evaluation of the likely scientific benefits to be gained from a research proposal against the likely adverse effects to the animals, although these are not the only factors that are taken into account (see paragraph 3.58–3.60 and 13.16).

2.27 In 2001, the European Commission decided to revise Directive EEC 86/609, and a Technical Expert Working Group was subsequently convened. It has recommended a number of ways in which the Directive should be revised.[38] These revisions, which are currently under discussion, would be binding for all EU Member States (see paragraph 13.47). They include

33 In early 2005 the owners and some of their neighbours applied for an exclusion zone around the farm, which was subsequently not granted by a judge. Instead, orders to regulate protests were imposed. The ruling judge said protesters had conducted a 'guerrilla campaign of terrorism', referring to actions taken against both staff and associates of staff. For example, it was reported that a petrol bomb and death threats had been delivered to staff and to the owners' family in March 2005. See BBC News (2005) *Activists branded as 'terrorists'*, available at: http://news.bbc.co.uk/1/hi/england/staffordshire/4184753.stm; BBC News (2005) *Activists 'no-go' zone rejected*, available at: http://news.bbc.co.uk/1/hi/england/staffordshire/4356713.stm; BBC News (2005) *Guinea pig farm's family targeted*, available at: http://news.bbc.co.uk/1/hi/england/staffordshire/4342183.stm. All accessed on: 14 Apr 2005.

34 Directives of the EU are binding law for the EU Member States. This is not the case for Conventions of the Council of Europe, which usually have the status of multilateral treaties (see paragraph 13.39).

35 In 1979, two Private Member's Bills were introduced. The Fry Bill was drafted by the RSPCA and had the support of many other animal protection groups. In contrast, the Halsbury Bill was drafted by the RDS and supported by a great number of scientific organisations. Both bills went through to the committee stage, and the Halsbury Bill stimulated the Lords to have a Select Committee examine the issue in detail. When the Conservative Government was elected in 1979, it agreed to update the 1876 legislation, which, it was widely acknowledged, was not well suited to regulating research a full century after it had been passed.

36 For a more detailed discussion of the background to the A(SP)A see Ryder RD (2000) *Animal Revolution: Changing Attitudes Towards Speciesism* (New York: Berg Publishers); Radford M (2001) *Animal Welfare Law in Britain: Regulation and responsibility* (Oxford: Oxford University Press).

37 Although the A(SP)A does not mention the term cost-benefit analysis, the term is commonly used to refer to Section 5(4), which states that: 'In determining whether and on what terms to grant a project licence the Secretary of State shall weigh the likely adverse effects on the animals concerned against the benefit likely to accrue as a result of the programme to be specified in the licence'.

38 European Commission Directorate General for the Environment *Laboratory Animals*, available at: http://europa.eu.int/comm/environment/chemicals/lab_animals/revision_en.htm. Accessed on: 14 Apr 2005.

a formalisation of the cost-benefit assessment, which would encapsulate in European law the approach that underlies the 1986 UK legislation.

## The context of the current debate in the UK

2.28 The history of the debate on animal research in the UK has been characterised by conflict, dialogue and cooperation. It has involved campaigners, representatives of animal protection organisations, physicians, scientists, those engaged in animal care and members of the general public. Despite differences on matters such as whether or not specific types of animal research are acceptable, opinion polls commissioned by various organisations concur in their finding that most people perceive a need for more information.[39]

### *The importance of openness and transparency*

2.29 The underlying assumption of most Western states is that a system of representative democracy is the most appropriate model to devise policies that are compatible with the wide range of views held by members of the public. Nonetheless, controversies remain in many areas, and parliamentarians and policy makers are required to justify their decisions, especially in areas where there is no consensus. In order to keep the public committed to democratic institutions and processes, all stakeholders need to have, as far as possible, access to relevant information (see Box 13.4). It is also necessary to offer credible and legitimate opportunities to contribute views that policy makers should consider in their decisions. An atmosphere of openness and transparency is crucial in this respect.

2.30 Until recently, most scientists were reluctant to engage with the public. Some have had concerns about the possibility of becoming victims of aggression. Others may have decided that explaining or justifying their research to lay people was unnecessary. Currently, there is a small, but increasing number of academic and industrial scientists, and scientific institutions involved in animal research who are more willing to engage in public debates about their work, particularly in relation to ethically sensitive matters. They take a proactive stance in explaining their research, the reasons for conducting it and the beneficial outcomes that they anticipate for society.[40] For example, the Roslin Institute, whose researchers cloned the sheep Dolly in 1996 (see paragraph 5.28–5.29), invited representatives of the press and the public to visit its laboratories, in reaction to the controversies about research involving reproductive cloning. The Institute also aims to increase knowledge about animal research among non-scientific or non-technical staff who interact with the local community. The CRO HLS has also generally increased openness. When a new senior management team was appointed in 1998, several measures were adopted in recognition of the fact that until then there had not been sufficient engagement with the public. Visits are now regularly organised and have included local groups, schools and colleges, as well as Members of Parliament. All visitors are usually invited for a tour of the animal facilities. The company has also been involved in several television documentaries in which members of staff have given interviews. We welcome such initiatives. They help to improve understanding about issues raised by animal research and reduce secrecy and lack of transparency, which are frequently associated with animal research and which pose a major

39 MORI (2002) *The Use of Animals in Medical Research*, Research Study Conducted for The Coalition for Medical Progress, p8, available at: http://www.mori.com/polls/2002/pdf/cmp.pdf. Accessed on: 14 Apr 2005; MORI (1999) *Animals in Medicine and Science*, General Public Research conducted for Medical Research Council, p34, available at: http://www.mori.com/polls/1999/pdf/mrc99.pdf. Accessed on: 7 Apr 2005.

40 See, for example, RDS *Welcome to RDS Online*, available at: http://www.rds-online.org.uk. Accessed on: 13 Apr 2005; See also Chapter 1, footnote 5.

41 See Chapter 15, footnote 16.

obstacle to informed debate. However, there is also a view that, in some instances, increased openness focuses disproportionately on the benefits of animal research, offering a 'sanitised' account which ignores the welfare implications and possible suffering of the animals.[41] Equally detailed information about both scientific benefits and implications of research for animal welfare is fundamental to achieving an informed debate. As a general principle, we conclude that freedom of information is essential to debate for its own sake. It would therefore be desirable for the public to have, as far as possible and subject to appropriate levels of safety for those involved in research, access to detailed information about the kinds of animal research, the number and species of animals used in specific research projects, the full implications in terms of pain, suffering and distress for the animals involved, and the intended benefits of the work. This information should be provided in a clear and accessible form. We consider ways in which such information could be supplied in more detail in paragraphs paragraphs 15.25–15.52.

## Summary

2.31 The justification for research involving animals has been contested for several hundred years. Since the mid-19th century, debate in the UK has intensified in parallel with the increased use of animals for this purpose. Growing levels of public concern led to the enactment of the first legislation on the subject in 1876. In the 20th century, academic discussion on the ethical justification of research involving animals, and debates bringing together stakeholder organisations, have been influential in the shaping of further legislation.

2.32 There is currently a broad spectrum of opinion about the ethics of conducting research on animals. A range of organisations is involved in the debate, including those representing the interests of industry and researchers, those who wish to improve conditions for animals or reduce research involving animals, and others who want an immediate end to research. Very few people resort to extreme forms of protest but their actions have had a disproportionate effect on the possibility of increasing openness in research. The current lack of openness and limited availability of balanced information appears to have contributed to mistrust. There is now increasing recognition by many stakeholders that this trend needs to be reversed.

# Chapter 3

## Ethical issues raised by animal research

# Ethical issues raised by animal research

## Introduction

3.1 As we have said, the debate about research involving animals ranges broadly over two distinct questions. The first asks whether animal research yields useful knowledge that could not be gained from other sources. The second concerns whether it is morally acceptable for humans to use animals in ways that can cause them harm. These two questions are clearly related: if it were the case that we learn nothing useful and distinctive from research that may harm animals, it would be difficult to see how, on any reasonable view, it could be morally justified. The question of scientific justification is therefore fundamental to the question of moral justification and we explore it in detail in Chapters 5–10.

3.2 However, a positive answer to the scientific question does not settle the moral question, for it may be the case that an experiment that yields useful and relevant information is not ethically acceptable. We need therefore to consider from first principles the arguments in support of, and against, research involving animals. For the purpose of our discussion, we take the principal ethical questions to be the following:

- Provided there are substantial benefits associated with animal research, why should the use of animals require special justification?
- Can any use of animals by humans be justified? Which specific issues need to be considered in the case of research?
- What role does the unavailability of alternatives play in the justification of research involving animals?
- How does the justification of such research relate to the justification of other uses, such as food production?
- What is the appropriate role of regulation for research involving animals?

3.3 For each of these questions, we consider commonly encountered arguments to bring clarity to the debate; to identify agreement where it exists; and to understand what lies behind remaining disagreement. We hope that this approach will be useful in enabling readers to make informed judgements about whether or not specific types of research, as described in Chapters 5–9, can be justified. We would also like to encourage them to reflect upon the assumptions behind their own positions and those of others.

### *Facts, values and the reflective equilibrium*

3.4 Historically, a number of apparently rigid and irreconcilable implicit and explicit ethical positions on animal research have arisen. Often, holders of these views think that their ethical judgement is irrefutably right, while that of others is simply wrong. Consequently, they consider truths about animal research to be self-evident, and suspect those who do not share these views of some sort of 'moral astigmatism' or intentional malevolence.

3.5 This state of affairs raises complex philosophical issues that are usually debated under the title of *moral epistemology*. The term refers to the study of, among other things, whether and how we can come to know moral truths; what we mean when we make moral judgements; and under what conditions we can change the moral judgements of others.[1] Although this Report is not suited to a detailed exploration of the many subtleties that

[1] See Campbell R (2003) *Stanford Encyclopaedia of Philosophy: Moral epistemology*, available at: http://plato.stanford.edu/entries/moral-epistemology. Accessed on: 11 Apr 2005.

characterise this subject, we think it important to draw attention to two fundamental issues relevant to our discussion.

3.6 First, the relationship between facts and values is not straightforward. A reasonable discussion between people of differing opinions requires clarity about whether the exact area of disagreement concerns:

- *knowledge of facts* (disagreement about whether or not a particular animal suffers from being used in a particular kind of research, or about the actual conditions of the research environment);
- the *interpretation of values associated with facts* (agreement that animals involved in a particular experiment experience pain, but disagreement about whether or not causing this pain is morally wrong); and
- the *way that values are derived from facts* (disagreement about whether or not animals are capable of being members of the 'moral community', and if they are, how we might know, see Box 3.1).

3.7 Secondly, even if the source of disagreement is identified, the question arises of what to do if one's own moral judgement is in conflict with new facts, evidence or arguments presented by others. On one view, such disagreement is unavoidable and, in principle, irreconcilable. Since facts are usually interpreted differently within frameworks of different ethical theories or belief systems, it is not surprising that proponents with different viewpoints will differ in their judgements. However, this is only true if ethical frameworks are construed as being unchangeable in principle. On a different view, new circumstances may enjoin us to test and, where necessary, revise our frameworks. This can apply to both proponents of particular ethical theories, as well as to people who have not considered ethical issues raised by animal research in a systematic way, but who nevertheless hold strong views. These processes of revision are sometimes described as striving to achieve a 'reflective equilibrium' which consists:

> '… in working back and forth among our considered judgments (some say our 'intuitions') about particular instances or cases [the relationship to judgments about similar cases], the principles or rules that we believe govern them, and the theoretical considerations that we believe bear on accepting these considered judgments, principles, or rules, revising any of these elements wherever necessary in order to achieve an acceptable coherence among them. The method succeeds and we achieve reflective equilibrium when we arrive at an acceptable coherence among these beliefs. An acceptable coherence requires that our beliefs not only be consistent with each other (a weak requirement), but that some of these beliefs provide support or provide a best explanation for others.'[2]

Thus, consideration of the many ways in which animals are used in research may require us not only to simply apply our system of beliefs to this specific matter but, in doing so, to accept the possibility that some parts of our belief system may require revision. Openness towards such a process would lead to more refined ethical theories and belief systems and it could also help identify possible policy reforms to generate practices that are acceptable to those holding a range of moral views.[3]

3.8 In this chapter, we generally do not take a view as to whether or not, and if so on what basis, particular arguments in favour or against the use of animals in research are justified. Rather, we comment on possible weaknesses of specific arguments and return to a more detailed outline of specific positions in Chapters 14 and 15.

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2 Daniels N (2003) *Stanford Encyclopedia of Philosophy: Reflective equilibrium*, available at: http://plato.stanford.edu/entries/reflective-equilibrium/#1. Accessed on: 11 Apr 2005.

3 See also Thagard P (2000) *Coherence in Thought and Action (MIT-Press).*

## Provided there are substantial benefits associated with animal research, why should the use of animals require special justification?

3.9 The primary reason given for using animals in research is to ensure scientific progress in basic and applied biological and medical science. Few people would deny that science is an important and powerful way of understanding the natural world. Methodical observations of evidence produced in carefully designed experiments have helped us to understand, for example, a great number of physical and chemical principles that govern biological processes. Many scientists argue that research involving animals is crucial in continuing progress.[4] As several respondents to the Consultation observed:

> 'If it is accepted, as it should be, that prevention of human suffering is a moral obligation, then the use of animals is unavoidable.'
> *Dr Chris Jackson*

> 'Man has the duty to treat sick people as well as save lives of people and animals. In order to do so, he must improve his knowledge of biology, and human and veterinary medicine. That is why man carries out animal research where there are no other appropriate investigational methods.'
> *ABPI*

> 'We do not feel it is ethical to subject humans…to these risks [the prolongation of disease or risk in toxicity testing] when there is a means to reduce them.'
> *Genetic Interest Group*

3.10 On the basis of these views it might appear that animal research requires no further justification. But, there are also people who assert that the use for harmful purposes of one species by another, without consent, is fundamentally unethical, regardless of any possible benefits, and that all forms of animal research must therefore be abandoned.[5] Instead, they argue that more effort should be made to find alternative ways of obtaining the required information, for example by undertaking research on human volunteers or on human tissue. Those who disagree assert that there are many significant research questions which can only be answered by using animals and that they are only used when absolutely necessary. They also question whether an abandonment of animal research, and the implied consequences, would be acceptable to all members of society. This situation leads us to two more specific questions. First, how important is the alleviation of human and animal suffering, in view of the fact that it may cause pain, suffering and distress to animals involved in research? Secondly, why should the use of animals in research be acceptable in cases in which it would be unacceptable to use humans? We address these questions next.

### *Is there an obligation to alleviate suffering?*

3.11 At the most fundamental level we can question why, in principle, there should be a moral obligation to undertake research to alleviate suffering in either animals or humans. Based on a particular view about the status of responsibilities that arise from things we do as opposed to things we do not do (i.e. 'acts versus omissions'), we could assert that there is no such duty. The argument would be that the strongest moral requirements are *negative*, relating to things which we should *not* do (omissions). Weaker *positive* moral requirements concern obligations in relation to things which we *should* do (acts). So, for example, we could argue that there is a strong obligation not to harm any child, but a far weaker one, possibly even

4 RDS *Welcome to RDS Online*, available at: http://www.rds-online.org.uk. Accessed on: 13 Apr 2005; see also Chapter 1, footnote 5.

5 BUAV *BUAV Today*, available at: http://www.buav.org/aboutus/index.html. Accessed on: 13 Apr 2005.

none, to give personal support to every child. If we apply this argument to the case of medical research undertaken to alleviate human suffering, we could infer that there is a strong obligation not to cause suffering, but a weaker one to alleviate it.

3.12 We agree that there is a plausible argument for morally relevant differences between specific kinds of action. While there may often be less forceful reasons for requiring acts in comparison to omissions, it does not, however, follow from this that there is *no* moral obligation to pursue research to alleviate suffering. First, the obligation may merely be less strong. Secondly, it could reasonably be argued that there exists a *prima facie* ethical duty to help alleviate suffering through acts, provided research efforts are in proportion to the extent of suffering to be alleviated. It remains unresolved at this stage as to whether such an obligation automatically sanctions the use of animals. The obligation relates primarily to the principle of alleviation of suffering, rather than to a prescription of specific ways in which suffering is to be relieved. In principle, the obligation might also be fulfilled by research that does not involve the use of animals, provided alternative methods are available.

***Is all research aimed at developing treatment for severe suffering that can only be alleviated through medicines?***

3.13 In the UK, approximately one third of all research involving animals is undertaken by the pharmaceutical industry to develop new treatments for a wide range of human diseases (see Chapter 8). Many would argue that, wherever the use of animals is scientifically unavoidable, it is ethically acceptable to use them. Some people may think that animal research is only undertaken to develop new medicines for serious diseases such as cancer or HIV/AIDS. While this is correct in several instances, consideration must also be given to the fact that pharmaceutical companies operate in a highly competitive sector. The need to generate profits may not always lead to the development of interventions that are most needed or reduce the greatest suffering, but may instead encourage the manufacture of those interventions that promise the highest returns. It has been suggested that animals are sometimes used in research where patient need is not clearly defined, for example, in the development of medicines that are thought to differ only marginally from existing products.[6] It is therefore important to ask whether products that are developed always justify the use of animals. One respondent to the Consultation also questioned whether the use of animals in pharmaceutical research was justified in view of the fact that:

> 'Many of the known human ailments are caused via humans not leading healthy lifestyles…'
> *Francis H Giles*

3.14 The argument that the suffering induced by animal experimentation is always outweighed by the fact that the burden of human disease is reduced by new pharmaceutical interventions can therefore lead to over-simplifications. Human health is affected by a spectrum of different kinds of disease and consequent suffering. The justification of animal research is more difficult when the disease in question could be avoided by appropriate human behaviour. It may be more straightforward where diseases emerge spontaneously and are independent of human behaviour. Thus, generalisations about the necessity of using animals are often unhelpful. In some cases animal suffering is weighed directly against human suffering; in other cases the reluctance of patients to achieve health improvements by changing their behaviour needs to be considered, as well as the pressures on

6 However, others claim that incremental improvements in the safety, efficacy, selectivity and utility of medicines are highly beneficial for patients and consumers. See Wertheimer A, Levy R and O'Connor TW (2001) Too many drugs? The clinical and economic value of incremental innovations *Investing in Health: The Social and Economic Benefits of Health Care Innovation* **14**: 77–118, Executive Summary available at: http://www.npcnow.org/resources/PDFs/executivesummary_toomanydrugs.pdf

7 Specific issues raised by the fact that not all research has immediate applications are considered in paragraph 3.53.

pharmaceutical companies to maximise commercial revenue.[7] Lastly, as we observed above, pharmaceutical research accounts for approximately one third of animals used. Research is also undertaken in the context of basic research (30%, see Chapter 5) and toxicity testing (16%, see Chapter 9), which require different kinds of justification (paragraph 3.53).

***'Engaging in research is a part of human nature'***

3.15 We need to consider one further argument that is relevant to our exploration of the need for the justification of animal research. Some people assert that it is an essential trait of humans to strive for knowledge through methodological enquiry. Hence, independent of the value of the results of research, it could be argued that research activity itself holds significant intrinsic value. For those who hold this view, undertaking research, including that involving animals, can be equated with the value of foraging for apes and nest-building for birds. They might therefore argue that it would be wrong to expect humans to cease undertaking animal research, because it is part of their natural behaviour.

3.16 Arguments based on 'naturalness' have considerable currency in the debate about animal research. However, there is disagreement about the usefulness of notions of naturalness (paragraphs 3.24–3.26). It is also questionable whether the alleged natural drive for humans to undertake research and advance knowledge would be irredeemably frustrated if they refrained from using animals. One respondent to the Consultation observed that 'necessity is the mother of invention', and hence it could be argued that if there was a political will not to use animals, human creativity might produce other solutions to achieve the same research goals.

3.17 It would appear that arguments about the loss of opportunities in both scientific research and gaining knowledge would only be forceful where, for compelling logical, ethical or pragmatic reasons, there was no possibility to obtain specific information using non-animal methods (see paragraphs 3.63–3.66). For example, it could be contended that it would be neither pragmatically feasible nor ethically permissible to produce inbred strains of humans for genetic knock-out studies (see paragraph 5.20). However, in an ethical discussion we might ask what exactly are the reasons that appear to make it ethically permissible to use mice, but ethically wrong to use humans, for genetic knock-out studies. We therefore now turn to the second question introduced in paragraph 3.10.

***Why should the use of animals in research be acceptable in cases where it would be unacceptable to use humans?***

3.18 Several respondents to the Consultation expressed their concerns about the view that convenience or scientific necessity are sometimes seen as sufficient reasons for using animals in research:

> 'I feel that any living creature should be given the same level of compassion as any other. Thus if it is unacceptable to conduct research on a human being, I feel that it is also unacceptable to conduct said research on any other living creature…'
> *Gaynor Armitage*

> 'We believe that all living things have the same moral status.'
> *Claire Hardman and Tom Schoeffler*

> 'a) Animals *are not* like us. But then the information gleaned from research conducted involving them would not be useful to humans, so
>
> b) Animals *are* like us. Which makes it ethically wrong to involve them in research.'
> *Kate White*

'When we consider a type of cost that both humans and animals are capable of bearing, such as the experience of suffering, do they count the same? If not, what is the justification for counting animals' interests less – and how can this be done without begging the question against the growing ranks of people involved in this area who believe that the comparable interests of humans and animals are equally important?'
*Professor David DeGrazia*

3.19 Those who accept the use of animals in research where the use of non-consenting human participants would be unacceptable could seek to develop and set forth a number of arguments supporting their case. For example, they could argue that animals are somehow morally less important than humans; that, when compared to humans, it matters less to animals to be used in research in certain ways; or that, although it would be preferable for animals to be free to live their lives, some research questions are so significant that the use of animals can be justified although this constitutes a wrong. Clearly, these options require us to consider a wide range of issues, ranging from abstract discussions about the moral status of humans and animals to more concrete comparisons of how animals are treated in other contexts. We discuss these in more detail below.

## Can any use of animals by humans be justified? Which specific issues need to be considered in the case of research?

### *The moral status of different beings*

3.20 It is common to begin reflection on the human use of animals by considering their relative *moral status* or moral importance (see Box 3.1). Within the current debate, we can identify three general positions, as follows.

- According to the first, there is a categorical moral dividing line between humans and animals. Human beings have a moral importance that animals lack. This we can call the *clear-line view*, and it is based on the assumption that there is something special about humans or that all humans possess some morally vital property that all animals lack.
- A second view is that there is not so much a clear dividing line as a continuum or *moral sliding scale*, correlated, perhaps, with a biological sliding scale of neurological complexity. Here, it is argued that there is a hierarchy in which humans are at the top end of moral importance, followed by primates and, for example, rodents such as mice and rats, with zebrafish, fruit flies and single-celled creatures arranged towards the bottom.
- A third view is to emphasise that biological classification is not by itself sufficient to support claims about a categorical moral distinction between human and non-human animals. It could hence be asserted that humans and either all, or at least some, animals, such as those that are sentient, are *moral equals*. Accordingly it could be argued that it is wrong to subject any animal (or any animal that is sentient) to treatment that would be unacceptable in the case of humans.

### Box 3.1: Use of the terms 'moral community', 'moral importance' and 'moral status'

The discussion of the three different moral views outlined in Box 3.2 introduces the idea that humans and animals could be described as having the same, or differing, *moral status*. This term, as well as other related important terms, requires some explanation.

For the purpose of this discussion we use the term *moral status* or *moral importance* to refer to the circumstance that a being is a member of a *moral community*. Members of a moral community include moral agents and moral subjects. *Moral agents* are beings that are able to behave in a moral way and are liable to moral criticism for any failure to do so. *Moral subjects* are beings whose features should be taken into account in the behaviour of moral agents (see paragraphs 3.31–3.32). Beings differ in their moral status if differences in their entitlement to certain liberties or goods can be justified in a morally valid way.

Moral agents are typically humans. There is some discussion as to whether animals are capable of behaving in moral ways. For example, there is evidence that some animals are capable of altruistic behaviour (see Box 3.2). However, the main discussion in this Report concerns the question of whether animals qualify as moral subjects. In this context it is useful to differentiate between *direct* and *indirect* reasons in support of such a view.

One indirect argument was proposed by Immanuel Kant. Within his philosophical theory, animals deserve the status of a moral subject and should be treated humanely not because they have a right to flourish, or to be protected from harm, but because those people who are cruel to animals are more likely to be cruel to humans*.

Others, however, put forward direct reasons in favour of viewing animals as moral subjects. They argue that the Kantian approach merely accords *instrumental moral value* to animals: animals are moral subjects because they can be used as an *instrument* for achieving the goal of making humans behave in a more moral way. Instead, critics argue that animals should be recognised as having inherent, or *intrinsic*, moral value. This view may be understood as saying that animals are valuable in themselves, that it matters to animals for their own sake how they are treated and that therefore their specific capacities need to be considered in interactions with them. The usual interpretation is that, as far as possible, animals should be free to live their lives without interference by humans.

In general, all moral agents are also moral subjects, but not all moral subjects are moral agents. Differentiating between moral agents and moral subjects does not necessarily imply that one group is morally more important than another. For example, humans who are severely mentally disabled are usually not capable of being moral agents. But this does not mean, without further argument, that they are morally less (or more) important than those humans who are capable of being moral agents. Nonetheless, it is commonly assumed that animals, if they are seen to qualify as moral subjects, are less important than humans. We consider the reasons behind these perceptions, which are reflected in the practices of most Western societies, in paragraph 3.21 and throughout this chapter.

* Heath P (Editor and translator) (2001) *Immanuel Kant: Lectures on Ethics* Schneewind JB (Editor) (Cambridge: Cambridge University Press).

3.21 It could easily be assumed that the justification for using animals for research (and other uses) depends entirely on the question of the relative moral status of humans and animals. Then the defence of animal use would be the same task as showing that only humans have moral status, or that their status is in some way 'higher' than that of animals. But this assumption might be too simplistic. Suppose it was possible to establish that the clear-line view is true and that all humans are more important moral subjects than all animals. Yet, this is not enough to show that animals can properly be sacrificed for human purposes. For it may be that although humans are morally more important than animals, they have a moral duty of *stewardship* to 'lesser' beings, rather than a right to treat them as they please, as implied by one respondent to the Consultation:

> 'The greater power of humans over other species brings with it a duty of care and compassion, not a licence to abuse.'
> *Alan St. John*

Therefore, the permissibility of harmful animal research does not follow by necessity from the assumption that humans have a higher moral status than animals.

3.22 Similar arguments apply with respect to the sliding-scale view: although a hierarchy of importance of different animals seems intuitively plausible to many people, it faces the same challenge of the stewardship argument posed against the clear-line view. Despite its initial attractiveness the usefulness of the hierarchy is also called into question when one wishes to consider the acceptability of different types of research. For example, how should the following four types be ranked:

i) research involving mice with no, or very minor welfare implications;

ii) research involving primates with no, or minor, welfare implications;

iii) research involving mice with substantial welfare implications; and

iv) research involving primates with substantial welfare implications?

According to the sliding-scale view, the order of acceptability ought to be i, iii, ii, iv. However, for many people, the order i, ii, iii, iv, as presented above, would seem more plausible, suggesting that an unmodified version of this view is less attractive than initially assumed.

3.23 With regard to the moral-equality view, it needs to be remembered that even if humans and animals are considered to be moral equals, it does not necessarily follow that harming animals in research should not be carried out. Moral equality is simply the doctrine that humans and animals are moral equals. In principle, this view could allow for the conclusion that harmful experiments should be conducted both on animals and humans.[8] Alternatively, the use of animals might be justified for practical reasons. For example, the reproduction rate of humans can be too slow for some experiments, or obtaining the quantity of a test chemical to dose humans could be impossible. Under these circumstances, it might be more appropriate to experiment on mice and rabbits, even if they are perceived as moral equals. Finally, it could be argued that where research has a negative effect on welfare and animals are less affected than humans, it is preferable to use animals to minimise the overall harm.

3.24 In conclusion, consideration of the relative moral status does not settle the question of the permissibility of animal research, or of any other use of animals, in a helpful manner. Although it is attractive to think that the question of justification is merely a matter of deciding whether the clear-line view, the sliding-scale view or the moral-equality view is the most adequate, this strategy may obscure more than it illuminates. Some people agree with this conclusion and refer instead to evolutionary theory as a justification of a relatively unrestricted right to use animals. Drawing on what can be termed *the competitive argument*, they may point out that different species must always compete for survival and that it is natural for any species to put itself first.

3.25 This argument is not compelling. The fact that humans have survived by dominating other species does not in itself show that we are morally justified in continuing to act in the same way. Humans have evolved a capacity to reflect upon their own behaviour. Much of this reflection has taken place by means of civilisation and especially education, which have channelled and changed 'natural' behaviour. Attitudes towards many forms of behaviour that were once justified as natural, as, for example, the dominance of men over women, or even the keeping of slaves, have changed substantially in a great number of societies (see also Box 3.4). Moreover, as we have said, if humans do indeed have a higher nature, this could entail duties of protection and stewardship for lesser beings, rather than the right of dominion (see paragraph 3.21).

3.26 Hence, it is clear that the competitive argument, which is based on the evolutionary order or the naturalness of certain behaviours, is unpersuasive in justifying ethically why it should be permissible for humans to use animals for research. It is crucial to distinguish between moral and scientific questions. Although, in particular cases, science may support particular moral conclusions, it can never be sufficient in itself to settle a moral question. Any argument for a moral conclusion needs to be based on moral premises or assumptions, although it may also draw on facts, including scientific ones. Understanding the relationship between the moral and the scientific questions is vital to achieving clarity in this discussion (see paragraph 3.6).

8 Of course, humans *do* participate in medical research (see paragraphs 8.25–8.28 and box 11.1) but generally it is not harmful and takes place with prior, voluntarily given consent.

***The relationship between moral status and morally relevant features***

3.27 Given that neither discussion about the moral status of animals and humans nor reference to the facts of evolution appears to provide a straightforward answer to the question of the permissibility of animal research, it may seem unclear how the debate could be advanced. In the following paragraphs, we suggest that a promising approach may be to ask what *features* of humans and animals could qualify them as a moral subjects (see Box 3.1), thus imposing constraints or limits on how they may be treated. We do not start from the assumption that there is one 'master property' or overriding criterion which determines how beings may be treated. Similarly, for the purpose of this discussion, we do not assume that there are some species that should never be used for any purpose, nor that the acceptability of using species depends on how closely related they are to humans in evolutionary terms. Rather, we explore the possibility that there are five features, at least one or all of which may be applicable to specific animals, albeit to differing degrees, and with subtly distinct moral consequences:

- sentience;
- higher cognitive capacities;
- the capacity to flourish;
- sociability; and
- the possession of a life.

We then turn to the second, and perhaps more difficult step, which concerns the question of deciding how such characteristics should be taken into account in moral decision making (paragraphs 3.51-3.57).

Sentience

3.28 An emphasis on sentience is most commonly associated with the utilitarian philosophy of Jeremy Bentham (see Box 3.3). Sentience, for Bentham, was usually understood as the capacity to feel pleasure and pain. Although the ascription of such states is not always straightforward (see paragraph 4.2), it is now uncontested that many animals are capable of feeling pain. Equally, it is uncontested that to cause pain is morally problematic and so needs to be taken into account in moral reasoning. This is the case whether the pain is suffered by a human or by any other sentient being.

3.29 However, some argue that the human experience of pain is in some relevant sense different from that of animals. It may be more intense because of a greater facility of humans to anticipate pain, or because of the disruption to social relationships that humans can suffer, for example if one member of a family suffers chronic pain. This is sometimes seen to lead to the conclusion that it might be more justifiable to use animals rather than non-consenting humans in harmful research. An alternative argument might be that humans are far more able than animals to cope with pain and suffering, especially when they understand the underlying reasons or purposes. This could suggest that beings with less-developed rational capacities are not necessarily suffering less, but more, since they are not in a position to conceptualise pain or suffering as means to ends (see also paragraph 4.17).

9 See also Ryder R (2001) *Painism: A modern reality* (London: Open Gate Press).

Higher cognitive capacities

3.30 Besides the ability to feel pain, many animals are also capable of higher cognitive capacities. Some of these appear to have great moral relevance in addition to any possible intensification of pain to which they might lead. They include: knowledge of good and evil (associated with Plato), possession of self-consciousness (Rene Descartes), possession of freedom (Jean Jacques Rousseau) and possession of a rational will, in the sense of being able to act according to self-set rules to achieve certain ends, including acting in a moral manner (Kant).

3.31 As we have said, there is a need to distinguish between a *moral agent* and a *moral subject* (see Box 3.1). Some higher cognitive capacities are clearly relevant to *moral agency*, since only a being capable of some of them, such as knowledge of right and wrong, may be a moral agent, subject to moral praise or criticism for its actions. The capacity for moral agency is also relevant with regard to the circumstances under which such beings can be wronged. For example, involving a moral agent who is capable of giving consent to potentially harmful research against his or her will is commonly regarded as violating a fundamental ethical principle.[10] A *moral subject* may lack the capacity for full moral agency, but may have other ways of expressing dissent or consent to certain treatments, for example by seeking to flee (paragraph 3.34).

3.32 Higher cognitive capacities, such as the use of language or the ability to act according to plans, can be understood as signs of intelligence. Some would say that these attributes are exclusive to humans. The discussion about whether or not animals possess such characteristics is controversial, not least because it is often closely linked to the question of whether or not an animal qualifies as a moral subject, or even as a moral agent. Some philosophers claim that, independently of any empirical research, it is self-evident that no animals other than humans have morally relevant cognitive capacities.[11] However, research combining philosophical and biological expertise has significantly increased knowledge about the cognitive capacities of the great apes, and other animals including dogs, rodents, birds and fish (see Box 3.2).

3.33 Some animals are able to learn complicated tasks, such as making and using tools. There is also evidence that they engage in non-trivial forms of communication and are able to coordinate social behaviour.[12] In animals such as monkeys, chimpanzees and bats, the rules of social interactions have been explored in more detail and have been described as primitive moral systems (see also Box 3.2).[13] Many of these characteristics had previously been thought to apply exclusively to humans, and they were often referred to in support of claims for special moral treatment for humans. Thus, somewhat ironically, some kinds of animal research have undermined claims of the uniqueness of humans and have instead demonstrated that humans and animals share certain morally relevant properties and capacities.

10 The ethical consensus is reflected in important international guidance on medical research, such as the World Medical Association's *Declaration of Helsinki*, which developed the principles established in the *Nuremberg Code*.

11 See references to Caruthers, Allen C (2004) *Animal Consciousness* (Stanford Encyclopedia of Philosophy), available at: http://plato.stanford.edu/entries/consciousness-animal/. Accessed on: 18 Apr 2005.

12 Riede T, Bronson E, Hatzikirou H and Klaus Zuberbühler (2005) Vocal production mechanisms in a non-human primate: morphological data and a modelJ Hum Evol **48**: 85–96.

13 See Patterson F and Gordon W (1993) The case for the personhood of gorillas, in *The Great Ape Project: Equality beyond humanity*, Cavalieri P and Singer P (Editors) (London: Fourth Estate), pp58–9. However, there is also some scepticism about such claims, see for example Wynne CDL (2004) *Do animals think?* (Princeton and Oxford: Princeton University Press).

## Box 3.2: Cognitive capacities of animals

***Communication***

Chimpanzees communicate through vocal sounds, facial expressions, postures and touch. They have an elaborate hierarchal social structure and use a complex communication system. For example, they alert other chimpanzees to the whereabouts of food sources with grunts and barks.*

***Tool use***

Tufted capuchin monkeys have been observed in the wild using stones to dig in the ground to forage for food and to crack seeds.† In captivity they have been observed carrying probing tools to a fixed apparatus baited with syrup in order to obtain the syrup.‡ Great apes are competent tool users in the wild as well as in captivity. For example, captive chimpanzee mothers have been observed showing their infants how to selectively use tools for tasks such as obtaining honey from a container.∫ Other monkeys have been observed washing food, such as potatoes, in the sea, in order to make them more palatable.**

***Intelligence***

Dogs have been shown to know the names of many objects by retrieving them as instructed. For example, a border collie called Rico was shown to be able to associate words with over 200 different items and make hypotheses about the meanings of words. Rico could correctly retrieve a new item from among a selection of eleven items already known, by inferring that the word mentioned did not refer to any of the ten items already known.†† Rats and mice perform tasks that make sensory, motor, motivational and information processing demands. Rodents are able to navigate in mazes or find platforms hidden in coloured water.

***Social behaviour***

Reciprocity is commonly seen within groups of capuchin monkeys and chimpanzees, involving behaviours such as food sharing, grooming and cooperation.‡‡ These activities are not always restricted to family members, but also extend to unrelated animals (non-kin reciprocity), as has been shown in research on bats.∫∫

In a study which observed capuchin monkeys, monkeys were shown to have a sense of 'justice'. They reacted badly if they saw another monkey receiving more preferred food than they did. The reaction took the form of non-cooperation with the research task, or a refusal to eat the less-preferred food that they were offered (which was otherwise acceptable if another monkey was also given this food item). The monkeys, however, did not react against the other monkey that was given the preferred food, but rather against the task that they would usually complete.¶

There are also examples of situations when animal behaviour has been interpreted as altruistic towards humans. For example, in 2004 a group of swimmers reported that a pod of dolphins protected them from a great white shark off the coast of New Zealand.¶¶ In 1996 an eight-year-old Western lowland gorilla Binti Jua carried a three-year-old child who had fallen into the animal's enclosure at Brookfield Zoo in Chicago, USA, to zoo keepers and paramedics, warning off another gorilla that was approaching. Other species have been observed showing signs of severe distress following the loss of an infant or parent, such as carrying the body around for several days, withdrawing from their group or appetite loss (see paragraphs 4.13 and 4.32).

* See, for example, The Jane Goodall Institute *Chimp Calls*, available at: http://www.janegoodall.org/jane/study-corner/chimpanzees/chimp-calls.asp. Accessed on: 18 Apr 2005.

† Moura ACdeA and Lee PC (2004) Capuchin stone tool use in Caatinga Dry Forest *Science* **306**: 1909.

‡ Cleveland A, Rocca AM, Wendt EL and Westergaard GC (2004) Transport of tools to food sites in tufted capuchin monkeys *(Cebus apella) Anim Cogn* **7**: 193–8.

∫ Hirata S and Celli ML (2003) Role of mothers in the acquisition of tool-use behaviours by captive infant chimpanzees *Anim Cogn* **6**: 235–44.

** See De Waal F (2001) *The Ape and the Sushi Master: Cultural reflections of a primatologist* (New York: Basic Books).

†† Kaminski J, Call J and Fischer J (2004) Word learning in a domestic dog: evidence for 'fast mapping' *Science* **304**: 1682–3.

‡‡ See Brosnan SF and de Waal FBM (2002) A proximate perspective on reciprocal altruism *Hum Nat* **13**: 129–52.

∫∫ Wilkinson GS (1990) Food sharing in vampire bats *Sci Am* **262**: 76–82.

¶ Brosnan SF and de Waal FBM (2003) Monkeys reject unequal pay *Nature* **425**: 297–9.

¶¶ BBC News (2004) Dolphins prevent NZ shark attack, available at: http://news.bbc.co.uk/1/hi/world/asia-pacific/4034383.stm. Accessed on: 18 Apr 2005.

3.34 Nevertheless, the degree to which animals of different types are capable of expressing higher cognitive capacities remains highly contentious. Clearly, though, it seems that in behavioural terms many animals are capable of demonstrating dissent by attempting to flee. It can therefore be argued that the implications of an animal's inclusion in an experiment that it seeks to evade is something that should be taken into account. At the same time, we should hesitate before drawing the opposite conclusion: that an animal that takes part apparently willingly does so freely. Participation can be achieved through training, which most likely lessens the possible stressfulness of research, but cannot be taken to mean the same as consent given freely from a competent human research participant. For example, an animal may have realised that cooperation with researchers is the only means of leaving a cage or pen, or gaining access to food, and it may 'agree' to take part for these reasons.

3.35 It is plausible to associate the ability to exercise higher cognitive capacities with neurological complexity. This is not to say that 'more-developed' animals are more important than 'less-developed' ones, but that there are more morally questionable ways of mistreating the more-developed animals.

3.36 Some object to a view in which moral status is based solely on higher cognitive capacities. This is because it appears that such views fail to offer grounds for refraining from causing unlimited pain or suffering to those beings that lack such capacities. But, as we have said, it cannot be taken for granted that any one of the morally relevant features that we consider here can be taken to be a master property. Rather, there are several reasons for showing moral concern, one of which is capacity to feel pain, which applies to many animals that do not exhibit higher cognitive capacities.

Capacity to flourish

3.37 A further basis of moral concern, associated with Aristotle, is the idea of animals having a *telos*, a good, or alternatively having interests or species-specific needs. If the animals are able to satisfy these needs, one might say that they *flourish*. This concept enables us to say that things may go well or badly for an animal depending on how specific environmental conditions relate to its usual species-specific development (see paragraphs 4.23–4.26 and 4.41).[14] If this view is not simply to be considered equivalent to those already considered (sentience and higher cognitive capacities), there must be a sense in which animals can flourish or wither independently of these features.

3.38 One way in which the concept might theoretically be extended is to focus not only on *avoiding* pain and suffering (which may require primarily consideration of sentience and higher cognitive capacities), but to consider also what environmental *enrichments* can be provided to attend to the species-specific needs. Animals may fail to flourish in laboratory conditions whether or not they experience pain, suffering or premature death.

3.39 While it may sometimes be difficult to determine when life is best for an animal, the concept seems to have clear force in relation to identifying circumstances that fundamentally violate the expression of significant biologically determined features of a species. For example, if animals such as dogs, which are a roaming species, are kept in very small and confined pens for prolonged periods of time, they would usually display stereotypic behaviours, which indicate that the animal is stressed. But keeping animals in unnatural environments need not always lead to welfare infringements. The relevant question to ask is not whether the environment is natural or not (in nature too, animals can encounter a number of adverse conditions) but whether it is appropriate with regard to its species-specific capacities and needs. Thus, if animals have been bred in captivity and are provided with a sufficiently complex environment, they may in principle be able to develop their potential in similar ways to animals living in the wild (see paragraph 4.26). In any case, the concept of flourishing can be seen as important as it establishes a more comprehensive idea of animal well-being than just freedom from pain and suffering.

3.40 Another extension of the concept of flourishing relates to considerations about the moral value of a *species*. This may be especially relevant to issues raised by selective breeding and the genetic modification of animals. These processes usually aim at altering an aspect of the genotype of a species in a targeted and often unprecedented way. In the context of basic

14 By species-specific development we mean behaviours and dispositions that the animal has developed during evolution in order to be able to respond to the range of situations typically encountered in its natural habitat.

research, a great number of experiments are now conducted in which single genes, or combinations of genes, are either introduced or deleted in research animals, and the effects of these actions are then assessed in order to increase understanding about genetic and associated developmental processes (see paragraphs 5.20 and 7.5). A spectrum of views on GM animals was reflected in the responses to the Consultation, for example:

> 'Animals should under no circumstances be genetically modified. It is going against nature, is dangerous…, and the animals… are often born mutated and are in pain and misery however long their lives.'
> *Ms Jenny Williams*

> 'Genetically manipulating and cloning animals breach the intrinsic value of each animal species and is ethically unacceptable…. Genetic modification is clearly promoting an increase in animal use…'
> *The Dr Hadwen Trust for Humane Research*

> 'GM animals… raise issues of commodification: should we modify animals to make them more economically productive? Discourses of 'natural' and 'unnatural' provide dubious grounds from which to stand within an ethical argument.'
> *Dr Richard Twine, UK*

> 'GM animals have already proven enormously valuable in biomedical research, in many cases facilitating a reduction in the number of animals used in medical research.'
> *The Bioindustry Association*

3.41 Genetic modification is a subject of considerable moral debate. Many members of the scientific community would deny that most cases of GM animals are more 'unnatural' than conventionally bred animals, or that the technique compromises the flourishing of animals in new and special ways. They point to the fact that selective breeding of animals dates back to the beginnings of agriculture and domestication, and that it has been used extensively within scientific research; for example, to create inbred strains of genetically identical animals or to sustain scientifically interesting mutations. Practically all conventionally bred animals used in agriculture, research or kept as pets are unnatural in the sense that they represent carefully selected genotypes from within a wide range of genetic variation that exists in the species. Proponents of this view also argue that there is no substantial difference in principle between more traditional forms of genetic selection and genetic modification;[15] that any animal produced through genetic modification could theoretically also have been created by means of selective breeding; and that the main difference is that genetic modification is faster and more precise.

3.42 While some of those who do not share this view might agree that arguments for species integrity are not straightforward, they may challenge the suggestion that no new issues are raised by the GM approach. For example, they may assert that the more gradual processes of selective breeding enable researchers to detect possible welfare-related problems at an earlier stage, as such problems may manifest themselves in smaller increments, and can be assessed against known strains of animals. By contrast, the 'sudden' introduction of a distant gene in a new organism by the GM method may lead to unexpected and unpredictable implications for welfare, especially in mutagenesis, 'knock-out' and 'knock-in' studies (see paragraphs 4.57 and 5.20–5.23). Although most researchers consider that the vast majority of such studies do not have any negative consequences for the animals involved, the

15 The Royal Society (2001) *The use of genetically modified animals* (London: The Royal Society).

evidence so far is inconclusive (see paragraph 4.57). The GM approach may also lead to very considerable increases in fetal mortality, and high levels of 'wastage' of animals that fail to develop the desired mutations (paragraph 5.23).

3.43 Alternatively, opponents to the GM approach might agree that the technique does not differ fundamentally from some forms of selective breeding, but consider that it amplifies the problem of deliberately interfering with a species' genotype in ways that can cause harm. If these observations are correct, the moral discussion then becomes focused on the extent to which genetic modification, and other forms of selective breeding, can be conducted without causing harm, as implied by the following response to the Consultation, which focuses on the *consequences*,[16] rather than the *act*, of modification:

> 'We…consider that it is unlikely that it matters, from the animal's point of view, whether any state of suffering was achieved by genetic manipulation or other means.'
> *AstraZeneca Pharmaceuticals UK*

Sociability

3.44 Another philosophical tradition, influenced by philosophers such as Karl Marx, Ludwig Wittgenstein and Martin Heidegger, sees sociability as creating a level of moral concern. According to this tradition, being a member of some form of complex community creates moral relations of rights and duties. The basis of such a community might be language or a substantial dependence on others for extensive social, economic or other reasons. But, if this tradition is not to be considered equivalent to the view of higher cognitive capacities discussed above, simply with the additional observation that these capacities develop through complex social interaction such as language use, then it must be sociability itself, rather than socially developed attributes, that generates moral concern.

3.45 This approach is plausible in that at least some rights and duties emerge in the context of social cooperation. But the argument can be developed in more than one way. One version has been highlighted in the following response to the Consultation:

> 'There are…animals which have established links with us and come to share our lives and our fate in historically complex ways – particularly dog, cat and horse. I think these links should be respected, even if the animals themselves have no knowledge of them or of their social and cultural significance. For, in disrespecting these links, we disrespect ourselves.'
> *Roger Scruton*

The view that humans have special responsibilities towards beings that form part of a community with them could also explain why some people have a special affinity for pets and working animals, and perhaps also why the A(SP)A requires special justification for the use of animals such as cats and dogs (see paragraph 13.5).

3.46 According to another version of the approach it could also be argued that not only the relationship to humans establishes certain responsibilities, but also relationships that animals have among themselves. This becomes perhaps most clear in considering animals such as primates. Since the species-specific capacities that these animals normally develop also include complex social interactions with other animals, many argue that expression of this behaviour is usually severely restricted in research.[17] Such infringements, it is feared, cannot be alleviated in the same way as physiological pain and suffering, the effects of which may

16 Other issues relating to the consequences of producing GM animals arise from the possibility that research animals, such as rodents, fish or insects, may escape and interbreed with wild animals, leading to potentially irreversible changes in the gene pool of the species. These issues are outside the scope of this Report.

be mitigated by pain relieving medicines (for a discussion of issues arising in relation to assessing pain and suffering in animals see Chapter 4). Although proponents of the use of primates would point out that housing of animals in groups or in pairs can allow for acceptable levels of welfare, opponents are often not persuaded. They argue that the cage sizes that can be provided in conventional laboratories will always be inadequate. There are also concerns about how these social animals might potentially experience the death of other research animals with which they have established relationships. Similar arguments could be made with regard to other social animals, such as dogs. It seems plausible that sociability may interact with other features in that, if social dislocation causes distress or suffering or interferes with flourishing to a significant degree, then the overall effect on the animal could be potentially serious.

Possession of a life

3.47 A perhaps more difficult morally relevant criterion is possession of a life. Is life itself of value? It may seem that if we think that killing is wrong, then we must be committed to the view that life itself is valuable. However, this need not be the case. Some philosophers have argued that life, as such, has no value, as distinct from the experiences that happen within life. Given this view, it is entirely reasonable to treat pain, suffering and other harms within a life with great moral seriousness without attributing a similar level of concern to death. For it can be the case that there are animals that have no sense of themselves as existing in time, although they may have highly developed capacities of sensory experience. In such cases it could be argued that to the animals concerned it matters less whether they exist but more how their moment-to-moment existence is characterised.

3.48 This line of thought raises the question of why we treat human life with special consideration and, in particular, why we experiment on animals precisely to find ways of prolonging the lives both of humans and animals. One possible answer, although not necessarily endorsed here, draws on two earlier points. First, most humans, and perhaps some other animals, exhibit self-consciousness and an ability to anticipate, reflect upon and fear their own death. Hence, the *prospect* of death usually has a significant secondary effect on the quality of lived experience. Secondly, humans, and perhaps some other animals, care about each other in the sense that the death of others is often considered a tragedy. Hence, death has special significance for highly social beings. It could therefore be argued that preserving the lives of humans and of relevant other animals should take precedence, with less regard being given to those animals that either lack self-consciousness or do not live in social groups.

3.49 A simpler response is to revert to an argument implied above according to which some higher cognitive capacity generates a right to life; most humans and those animals that closely share similar features in this respect have such a right, while other animals do not. Many attempts have been made to provide a philosophical foundation for this view, although none commands wide agreement (see paragraph 3.20 and Box 3.4).

17 See Smith JA and Boyd KM (Editors) (2002) *The Boyd Group Papers on The use of Non-Human Primates in Research and Testing* (Leicester: The British Psychological Society), available at: http://www.boyd-group.demon.co.uk/Prefaceandsummary.pdf. Accessed on: 18 Apr 2005.

Summary of the discussion about morally relevant features

3.50 We have suggested that the proper moral treatment of a being depends on the characteristics it possesses, rather than simply on the species to which it belongs.[18] In this regard, we have focused on sentience, higher cognitive capacities, capacity for flourishing, sociability and possession of a life. With the possible exception of the last feature, each provides reasons for moral concern, and hence it can plausibly be argued that animals in possession of one, or several, of these features are moral subjects, and that any treatment infringing on one of the features requires careful justification. The three initially attractive approaches often encountered in arguments about whether or not it is acceptable for humans to use animals for potentially harmful purposes (the *clear-line view*, the *moral sliding-scale view* and the *moral-equality view)* are therefore less helpful.

***The functional role of morally relevant features: absolute constraints or factors to be balanced?***

3.51 We have not yet considered what weight the individual morally relevant features should have in deciding the acceptability of research. To anticipate the discussion, let us consider the capacity to feel pain. There is little disagreement that this provides a clear moral constraint on how a being may be treated. But is it merely one factor to be taken into account, which is to be weighed against others? Or does it create an absolute protection on how the being may be treated, in the form of an inviolable right? These two possibilities are reflective of different philosophical approaches which are summarised in Box 3.3. Someone arguing from a *consequentialist view*, where the moral value of individual actions is based primarily on their outcome, would emphasise the first possibility, and accept a 'weighing' of different goods. A proponent of a *rights-based* or *deontological* view might argue in terms of the second possibility, asserting that certain factors establish absolute constraints, which 'trump' or 'outweigh' other factors (see Box 3.4). We now explore in more detail the three principal options of how to consider the morally relevant features in relation to animal research: the weighing of consequences (consequentialism); the setting of absolute prohibitions (rights-based) or incorporating elements of both in a hybrid approach.

[18] It could be argued that a focus on morally relevant features would also have implications for the treatment of humans who lack some, or all, of these features. For example, it could follow that embryos, some infants or severely disabled people could be used for research without consent by proxy. However, such inferences are not straightforward and require additional arguments. It could furthermore reasonably be argued that the involvement in research of humans who lack morally relevant features is not acceptable because such a treatment may be perceived as undignified by friends and family members, thus disrupting important social institutions. Trust in healthcare practitioners may also be eroded, and, for example, people might become afraid of hospital treatments, fearing that physicians will not always act in their best interest. Addressing the wider implications of approaches that draw on morally relevant features is beyond the scope of this Report.

### Box 3.3: Three paradigms of normative ethics

Normative theory is a branch of philosophical ethics which seeks to develop theoretical frameworks that can help to determine whether actions are right or wrong. Three important approaches are consequentialism, deontology and virtue ethics. Some take the view that they are mutually exclusive, and constitute competing frameworks. Others point out that they can be seen as overlapping and complementary, emphasising different aspects of the complex interactions of humans between each other and with the environment.

***Consequentialism***

According to this approach, the moral value of individual human actions, or rules for such actions, is determined primarily by their outcome. Such approaches do not usually put strong emphasis on the inviolable rights of moral agents or moral subjects. One important type of consequentialism is *utilitarianism*, developed most prominently by the British philosophers Jeremy Bentham and John Stuart Mill in the 18th and 19th centuries.* For utilitarians, the best actions are those that produce most overall happiness or pleasure (see paragraphs 3.52–3.55).

***Deontology***

The name of this theory is derived from the Greek *deon*, which means duty or obligation. In this theory, certain actions are right or wrong independent of their outcome. Instead, their rightness or wrongness is defined by a formal system, which defines certain actions as intrinsically right or wrong. Moral agents have a duty to respect the principles derived from this system and to act according to it. Rights of other moral agents or subjects can be violated if they are not treated accordingly. Historically, deontology is associated with the work of the German philosopher Immanuel Kant (1724–1804; see paragraphs 3.56–3.57).† A separate form of deontology advocates the concept of animal rights (see Box 3.4).

***Virtue ethics***

According to this approach, first developed by early philosophers such as Aristotle around 2,300 years ago, moral value depends less on the duty to follow rules given by formal systems, or on the duty to maximise beneficial consequences, than on the character of the moral agent. A virtuous moral agent is someone who deliberates and acts in a way which displays virtues such as justice, truthfulness and courage. According to this view, morality is closer to the exercise of a skill than the following of standardised formulae or rules.‡

* See Sinnott-Armstrong W (2003) *Consequentialism*, available at: http://plato.stanford.edu/entries/consequentialism/. Accessed on: 18 Apr 2005.

† See Johnson R (2004) *Kant's Moral Philosophy*, available at: http://plato.stanford.edu/entries/kant-moral/. Accessed on: 19 Apr 2005.

‡ See Kraut R (2001) *Aristotle's Ethics*, available at: http://plato.stanford.edu/entries/aristotle-ethics/. Accessed on: 18 Apr 2005.

### *Consequentialism*

3.52 In any approach that seeks to weigh consequences, a number of more detailed questions need to be considered, to establish whether justification of a particular form of animal research is possible. These are as follows:

i) The value of the goals of research:

Research may be undertaken to achieve various goals, for example to advance basic biological knowledge, or to directly improve medical practice. In evaluating research, it is important to ask: how valuable is the goal and for whom? How speculative might the gain be? (See paragraphs 3.9-3.19 and 5.4).

ii) The degree of harm experienced by animals:

This is dependent on the number of animals used, and their capacity to experience pain, suffering or distress or other adverse effects. The degree of harm relates, where applicable, to conditions during breeding, transport, housing and research-related procedures (paragraphs 4.31-4.59). The question posed is: what harm could animals suffer in pursuit of the research goals?

iii) The availability of alternatives to research involving animals:

Are there non-animal alternatives that could achieve the same research goal? If alternatives are not available, it would appear important to be able to assess the reasons why: are alternatives logically or conceptually unavailable, or are they unavailable because of political, financial, logistical or other practical reasons? (See paragraphs 3.63-3.66 and Chapter 11).

3.53 Before examining consequentialism in more detail, we need to discuss a special issue raised by point i) above, regarding the value of the goal(s) of research. Some people argue that a major distinction should be made between two types of research. They note that there is (a)

research that has the aim of benefiting human health, animals or the environment in a direct and immediate way, for example by assessing the safety of a new medicine or agrochemical such as a pesticide; and (b) basic research, sometimes also called fundamental, 'blue-sky' or curiosity-driven research. The primary aim of the latter is to increase knowledge rather than directly to decrease human suffering, but with the possibility that eventually the research could produce health-related benefits (see Chapter 5). Two general arguments are usually made when considering the value of basic research:

- The first is that it is difficult to assess the value of such research, because the advancement of knowledge can be difficult to predict. Several questions need to be answered, including (a) is knowledge produced simply by completing a research project or by disseminating the results widely, for example by publishing in peer-reviewed journals? (b) what is the likelihood of any useful application arising from knowledge gained in basic research? and (c) if results from a basic research project are viewed as being unlikely to contribute to any practical application, can the research be justified?
- According to the second argument, every scientifically sound research project involving animals is intrinsically valuable, since it contributes to the 'jigsaw puzzle' of scientific knowledge, i.e. to the sum total of scientific knowledge about a subject. Thus, whether or not a specific piece of research contributes directly to medical or other beneficial applications for humans, it will always have some intrinsic worth because of the knowledge gained. On the basis of this argument, it is considered wrong to measure the value of research purely in terms of its immediate benefits.

3.54 Consequentialist reasoning requires two steps: first, an identification of the harms and benefits considered relevant to moral justification and, secondly, a calculation of whether the course of action envisaged produces a higher balance of benefit over harm than any alternative feasible option. Note that it is not enough simply to cite speculative benefits. It is necessary to have an estimate of the probability of success (be this the generation of knowledge or the development of a new medicine), which will need to outweigh, in some sense, the estimated harm that the experiment will cause, if an experiment is to be justified on consequentialist grounds. Any such calculation will need to allow a way of comparing distinct costs and benefits in order to calculate what level of health benefit for humans would outweigh, for example, a particular pain experienced by animals involved in research.

3.55 One of the most commonly found consequentialist positions is utilitarianism. In its simplest form the approach establishes a social duty to maximise the balance of pleasure over pain (see Box 3.3). Utilitarianism requires careful consideration of the capacity of all beings capable of suffering, and permits animal (or human) suffering, if in sum, it causes more pleasure than pain. Where this is the case, the ends would justify the means. Thus, from the utilitarian view, the capacity for pain and suffering does not constitute an absolute constraint, prohibiting any negative interference. Nor does the approach usually associate inviolable rights with sentience. This is why contemporary utilitarians, such as Peter Singer, do not talk of 'animal rights' but of 'animal liberation'.[19] From the utilitarian viewpoint there is, in principle, no restriction of the goals of research, whether it be health benefits, idle curiosity or sadistic pleasure, as long as the overall sum of pleasure outweighs the overall sum of pain. Within the current debate, this extreme view, though often mentioned and theoretically possible, is probably not held. Most commentators appear to accept at least

[19] In his highly influential book *Animal Liberation*, Singer focused on cases of research that caused grave suffering to animals and had little discernible benefit. He did not explore in detail the question of whether medical research involving animals can be justified in utilitarian terms. However, this seems likely in at least some cases, provided the overall costs in terms of pain, suffering and distress caused by research are outweighed by the overall benefits in terms of alleviating and preventing pain, suffering and distress. See Singer P (1975) *Animal Liberation* (New York: HarperCollins).

some restrictions on the acceptable goals of research, i.e. there must be some health or scientific benefit. Unlike strict utilitarians, consequentialist defenders of animal research, therefore, accept such restrictions.

### *Deontological/rights-based approaches*

3.56 Those arguing within a deontological framework assert that at least some uses of humans and animals are absolutely prohibited (see Box 3.3). For example, according to an argument frequently set forth by theorists and campaigning organisations the capacity for sentience is not merely an input into a utilitarian calculus, but the basis of a *right* not to be subjected to pain and suffering, whatever the wider benefits (see paragraph 1.4). According to this view, any sentient being has a right not to be used purely as a means to the ends of others if to do so would cause it pain or suffering (see Box 3.4). Such an approach combines a utilitarian theory of value with deontological (duty-based) constraints on action and would appear to rule out all research involving animals that causes any degree of pain.[20]

#### Box 3.4: Speciesism and animal rights

Some people argue that the way many animals are treated in contemporary Western societies is morally objectionable. They draw an analogy to unjustified discrimination and exploitation in cases of racism and sexism, and argue that making membership of the moral community dependent on specific human traits alone amounts to 'speciesism'. Rejecting this view, they argue that a much wider circle of beings deserve to have their interests considered for their own sake, usually meaning all those beings that are able to suffer.*

Some of those who share the belief that society's current treatment of animals amounts to speciesism take the view that overcoming this form of discrimination requires that rights are ascribed to all animals. The criterion for whether or not a being deserves rights is frequently seen to depend on whether or not it is 'the subject of a life'. If, the argument runs, it makes sense to say of a being that it is conscious of its own existence, and that its own life is important to itself, it has intrinsic moral value (see Box 3.1). This moral value should then be recognised by the same rights accorded to humans, as, for example, set out in the United Nation's *Universal Declaration on Human Rights*. This raises the question of which animals are capable of being the subject of a life. Some argue that this is the case in animals such as the great apes,† but others would draw a much wider circle, including all animals capable of being sentient.

Many people reject the analogy between the humane treatment of animals on the one hand and racism and sexism on the other. They emphasise what might be called a 'psychological truth' which states that in cases where a choice has to be made, protecting the life or welfare of a human is a greater priority than a similar protection for an animal, just as one might also protect a family member rather than a distant stranger. A vital question is whether such preferences for humans in general, or those who are close to us, are strictly speaking immoral, and should be over-ridden by a comprehensive and all-inclusive moral system, or whether they are morally justified, as other philosophers have argued. There are powerful arguments on both sides, and no universally agreed answer. We return in Chapter 14 to the role that this disagreement plays in debates about the ethics of research involving animals.

* Singer P (1975) *Animal Liberation* (New York: HarperCollins); Ryder RD (2000) *Animal Revolution: Changing Attitudes Towards Speciesism* (New York: Berg Publishers); DeGrazia D (1996) *Taking Animals Seriously: Mental Life and Moral Status* (Cambridge: Cambridge University Press).

† See website of the Great Ape Project, available at: http://www.greatapeproject.org/. Accessed on: 19 Apr 2005; Cavalieri P and Singer P (Editors) (1993) *The Great Ape Project: Equality Beyond Humanity* (London: Fourth Estate).

3.57 Deciding between the 'weighing' (or utilitarian/consequentialist) view and the 'absolutist' (or rights-based) view may not seem easy. Some progress can be made by the simple observation that not all experiences of pain are the same. If pain is mild and short-term, it could plausibly be justified for the sake of other important benefits; even, arguably, in the case of human exposure to pain without consent. For example, forcing people to remain standing in cramped and highly uncomfortable conditions, in order to make room for the emergency services to gain access to an accident, would appear to be justified. However, if pain is severe and prolonged, with lasting effects, then matters seem quite different. Where to draw the line may be very difficult, but there could be room for a complex view in which different types of pain call for different types of moral response, in which some pains are permitted and others not, involving some weighing and some absolute prohibitions. Such an approach is found in what can be called 'hybrid frameworks', to which we now turn.

20 However, some observational research, usually of animals in their natural habitat, may be permitted.

***Hybrid frameworks***

3.58 Hybrid frameworks contain some elements of the consequentialist theory, and some of the deontological approach. Most views in the current debate are of this form, even if there is great disagreement about the details. One prominent example of a hybrid view, although in itself not explicitly a philosophical approach, is the current UK regulatory regime, which we discuss here briefly, both for its own sake and as an illustration of a hybrid view (Chapter 13 addresses regulatory aspects in more detail). The suggestion that the current UK regulations are hybrid may cause some surprise, as it is often assumed that in its use of a cost-benefit assessment current regulations are utilitarian. This is a serious philosophical error, as we shall see.

3.59 The current regulatory framework in the UK requires that any research on vertebrate animals (and the common octopus)[21] which may cause pain, suffering, distress or lasting harm must be licensed (see paragraphs 13.8-13.18). A licence is not required where no harm will be caused or when the research involves only invertebrates (excluding the common octopus). Harmful experiments for the sake of mass entertainment (such as television entertainment) are prohibited by law, and research involving animals for the production of new cosmetic ingredients is also not permitted (see paragraph 13.6).[22] Although not prohibited directly by law, licences for any research involving the great apes (gorillas, chimpanzees, pygmy chimpanzees and orang-utans) are not granted as a matter of current policy. In order for licences for specific research projects to be issued, the law requires that the likely benefits of the research, and the likely costs to the animals, are considered; that 'the regulated procedures to be used are those which use the minimum number of animals, involve animals with the lowest degree of neurophysiological sensitivity, cause the least pain, suffering, distress or lasting harm, and are most likely to produce satisfactory results';[23] and that there are no available alternatives to achieving the goals of the experiment without using protected animals (paragraph 13.17).

3.60 Pain and suffering of animals are treated with great seriousness in the current UK legislation. For example, licences may not be granted for research that is 'likely to cause severe pain or distress that cannot be alleviated'.[24] Where possible, potentially harmful research must be conducted under anaesthetic or with the use of pain relieving medicines. By contrast, animal death, if brought about without pain or suffering, is regarded as a far less serious matter. Animals that are not used in regulated procedures but killed humanely to obtain tissue samples or because they are surplus to requirements are excluded from the controls of the A(SP)A (see 13.26).[25]

3.61 In summary:

- The morally relevant features identified above (sentience, higher cognitive capacities, flourishing, sociability and the value of life) are all considered in the current regulations.

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21 More precisely, protected animals comprise all vertebrates and members of the common octopus species including fetal, larval or embryonic forms from the mid-gestational or mid-incubation period onwards for mammals, birds and reptiles, or in any other case, from the stage of development when the animals become capable of independent feeding.

22 Note that animal research for the testing of new household cleaners that differ insignificantly from already-marketed products is not prohibited.

23 A(SP)A, Section 5, 5(b).

24 Home Office (2000) *Guidance on the Operation of the A(SP)A 1986* (London: TSO), paragraph 5.42. This refers to Section 10(2A) and Schedule 2A of the A(SP)A which states that 'All experiments shall be carried out under general or local anaesthesia'. Exceptions exist when anaesthesia use is incompatible with the object of the experiment. In such cases, Schedule 2A (Article 8 of Directive 86/609/EEC) specifies that 'appropriate legislative and/or administrative measures shall be taken to ensure that no such experiment is carried out unnecessarily'. Schedule 2A was imposed on the A(SP)A by the (Amendment) Regulations 1998.

25 Schedule 1 of the A(SP)A sets out 'Appropriate methods of humane killing'.

- The current regulations combine deontological and consequentialist elements:
  - there is a *de facto* ban on the use of specific species, the prohibition of causing some forms of pain and certain types of research;
  - within the 'permitted' area, where reasons are weighed and balanced, the regulations are consequentialist but not utilitarian, placing restrictions on the type of goals that may be pursued.
- Licences are thus granted on a case by case basis where weighing of animal suffering in relation to the research goal is one aspect of the cost-benefit assessment, and where other considerations, such as deontological constraints, are taken into account.
- What some people might regard as costs, for example harm to most invertebrates or painless death, are not regulated in the UK.

3.62 We return in Chapter 13 to a more detailed discussion of the regulatory framework in the UK and, in Chapters 14 and 15, to further moral consideration. Here we conclude that there are several ways in which morally relevant features can be taken into account, depending on whether they are considered in the context of a consequentialist, deontological or hybrid framework. We have illustrated this analysis by focusing on the capacity for pain. It might also be possible to combine, for example, deontological frameworks with the morally relevant criterion of higher cognitive capacities, in which case animals that are merely capable of sentience might not qualify as moral subjects. These and other approaches would clearly require further development and justification, which is beyond the scope of this chapter. Our primary aim has been to illustrate the mechanism by which morally relevant features function in different frameworks.

## What role does the unavailability of alternatives play in the justification of research involving animals?

3.63 We have said that one of the important aspects in the ethical evaluation of research involving animals is whether the research goal could be achieved by other means, and, if not, what the reasons might be. One respondent to the Consultation remarked:

> '"By law in the UK, animals can only be used for research if there is no other way of obtaining the information" … If research on alternatives is not meaningfully supported by the Government, how is it possible to follow the law? How can an investigator know whether there is an alternative way of obtaining the relevant information if the study of alternatives is so poorly funded?'
> *Professor David DéGrazia*

3.64 We discuss the potential of alternatives in more detail in Chapters 11 and 12. For now, we note that this comment raises at least two important issues. First, alternatives are developed primarily by industry, academia and relevant charities. Although the UK Government also provides some funding for the development of alternatives (see Box 11.3), it may be especially important to be clear about its responsibilities concerning the development of alternatives as it is the authority that grants licences for the conduct of animal research, much of which is publicly funded. The Government also contributes significantly to the demand for animal research, for example, through regulatory requirements established by the Health and Safety Executive (HSE), Department of Trade and Industry (DTI) and other departments (see also paragraphs 13.48-13.52).

26 See Animal Procedures Committee (2003) *Review of Cost-Benefit Assessment in the Use of Animals in Research* (London: Home Office).

3.65 Secondly, in undertaking an ethical review of a research proposal in the light of available alternative methods, it can be useful to consider the reasons why other alternative methods are not yet available. Although from a regulatory and practical perspective it may be reasonable to take into account only those options that are currently available, this may be less acceptable for an ethical evaluation. It could be argued that a proposal for which alternative methods exist in principle (but have not yet been sufficiently developed for use because of, for example, financial or other constraints) should be deferred until the alternative method becomes available, in order to allow a comparison. The question of opportunity costs is then raised: how much does it matter that research is delayed? It would seem that the answer to this question would depend primarily on the value of the research goal and the welfare implications for the animal. There is also the more general question about the value of scientific enquiry *per se*, and some people would argue that, in principle, no delays are ever acceptable.

3.66 A related question concerning the possibility of delaying research to prevent the use of animals for some types of experiment is raised by the efficiency of alternatives. It may be the case that there are alternatives to specific research procedures, which refine or reduce the use of animals significantly, or replace it altogether, but which imply slower scientific progress. How should such options be balanced in an analysis of the costs incurred for animals and the benefits offered to humans? We examine these questions in Chapters 11, 12, 14 and 15.

## How does the justification of animal research relate to the justification of animals for other uses?

3.67 We have already noted the various ways in which humans interact with animals (paragraph 1.1). Comparing different uses of animals can be helpful in assessing more closely how specific morally relevant criteria, such as those considered above, are valued in practice. Comparisons usually carry with them the implication that the same criteria should be applied in comparable cases, and that similar cases should be evaluated alike. Two tendencies are common in making comparisons:

- 'Using animals in research is justified because we also use animals in other contexts'

  According to this view, a closer look at the way in which animals are used in, for example, food production and sport reveals that a range of negative implications for animal welfare in favour of human benefit are accepted by many people. Accordingly, the view might be taken that the use of approximately 2.7 million animals in research is relatively insignificant when compared to more than 950 million livestock and nearly 500,000 tonnes of fish used annually for food production in the UK (Appendix 1), or when compared to the number of wild birds and mice killed by pet cats, which has been estimated to be 300 million per year.[27] The benefit to humans in using animals as food entails primarily an increased range in dietary variety, while the benefits of animal research can consist in significant developments in scientific progress and human welfare. Hence proponents of this view assert that the latter use should be more acceptable.

- 'Thinking about animal research poses more questions than it answers'

  Here, it is argued that concerns about animal research show that, insofar as other practices involve comparable degrees of pain, suffering and distress, they are in fact not as widely accepted as is sometimes claimed. Discussion about animal research can thus enjoin us to reassess the basis on which we seem to accept other uses of animals: is it

27 The estimate by the Mammal Society that 300 million wild animals and birds are killed by domestic cats every year in Britain is based on a survey of the kill or capture records of 964 cats over a five-month period. See The Mammal Society (1998) *Look what the cat's brought in*, available at: http://www.mammal.org.uk/catkills.htm. Accessed on: 15 Mar 2005.

reasoned argument? Are other uses accepted because people do not really know how the welfare of animals is affected, or because they adopt an 'out of sight, out of mind' view? Or, for example, because they trust farmers more than scientists to treat animals well? With regard to the quantities of animals used in different contexts, it could be argued that, although the number of research animals is far smaller than the numbers of animals used, for example, in food production, their lives are usually shorter, and that they may experience greater degrees of pain, suffering or distress.

3.68 In comparing different uses of animals it is critically important to consider the worthiness of the goal, the suffering of the animals involved and the availability of alternative ways of achieving the goals for which animals are used (see Appendix 1). If well informed, such comparisons can be instructive in ascertaining the basis of justifications given for the use of animals. However, due to the many variables involved, acceptance of one use does not automatically justify other uses. Comparisons are necessary, but are not the only consideration in moral analysis. Each of the uses requires individual consideration and justification. We return to the question of comparing different uses of animals in Chapter 14.

## What is the appropriate role of regulation for research involving animals?

### *Two views about moral agency*

3.69 So far we have concentrated on the circumstances under which it may be acceptable to conduct harmful animal research. Our discussion has also briefly focused on what it means to be a moral agent (see Box 3.1). We now explore this concept in more detail, since it bears on the question of what it is to be a morally responsible scientist, and the role of regulation in generating a morally acceptable environment.

3.70 We can contrast two principal views concerning moral agency:

- According to the first, associated with Bentham and Kant, to be a moral agent is a matter of following a set of rules or principles.
- According to the second, associated with Aristotle, the requirements of moral agency cannot be formulated in terms of a precise set of principles, but rather they involve cultivating a certain set of dispositions of character, usually called virtues. These virtues are required in order to develop excellence in a practice or task (see also Box 3.3).

3.71 One motivation for virtue-based theory is that rules or principles will always be simplistic and thus may demand behaviour that is wrong or otherwise inappropriate. Virtue theorists argue that, if people can learn to become experts in making excellent judgements, then this ability is morally superior in comparison to blind obedience to rules, as well as leading to a better moral relationship between, in this case, humans and animals. This argument has significant implications for the appropriateness and nature of regulations. Regulations usually encode a rule-based morality, which might seem to be too inflexible and sometimes even morally counter-productive. It could be argued that the exercise of wise judgement by scientists is morally superior to mere conformity with regulations.

### *Should regulations be relaxed or tightened to achieve least risk and best moral practice?*

3.72 There are several arguments in favour of stringent regulation. One aspect concerns the current social trend towards a perceived need for accountability and transparency in all areas of public life. But, more importantly, when the activities of researchers were much less stringently regulated in the past, some were suspected of questionable attitudes and behaviour. Allegations included maltreatment of animals, lack of awareness of the capacity of animals to suffer and lack of realistic reflection on the likely benefits or probability of success of experiments (see paragraphs 2.12-2.13).

3.73 The crucial question now is not how scientists once behaved, but rather how we could reasonably expect them to behave if regulations were less rigorous. The existence of any regulation is justified in terms of reducing risks, and therefore we first have to consider what the consequences of non-regulation, or less-detailed regulation, would be.[28] Accordingly, scientists who consider that they are sufficiently experienced to judge the needs of animal welfare in the planning and conduct of their work might well argue that they now have acquired appropriate virtues. If this is correct, then the risk of making regulations less detailed would be small. Furthermore, consideration of ethical aspects forms part of the training of personal licence holders,[29] and is beginning to be included in college and university education in the life sciences. Some take the view that continuing developments in this area might be considered another good reason for relaxing regulation.

3.74 Opponents, however, might argue that scientists have developed virtues to the degree that they have, primarily *because of* the regulations. They assert that a strict regulatory framework encourages scientists to be proactive in seeking out and implementing humane practices. In a less-regulated world, they might let such virtues wane, especially as a scientist's priority is usually to make scientific progress, which may often, but need not necessarily always, coincide with ensuring the highest possible degree of animal welfare.

3.75 In this respect, it might be instructive to compare common Western approaches to a particular non-Western approach. Western practice usually focuses on beliefs and their consequences. An example of a different approach is that practised by Australian Aborigines, for whom the emphasis is on people and their relationships.[30] In the Western context, causing pain or suffering to animals is recognised by some as an offence to reason and is addressed by adopting a resolution to minimise harmful consequences, for example by applying Refinement, Reduction and Replacements. In the Aboriginal approach, the subject of any offence is considered to be another being, referred to as an 'I' or 'thou', and a ritual apology can sometimes be offered to an animal killed to provide food or clothing. The object of this process is to inform the spirit of the animal that the act has been done in order to survive. The apology is a quest to reweave a torn religious (literally binding) relationship.

3.76 Clearly, for the UK context, the Western approach to the conflict between human and animal interests is more practicable and therefore appears to be the more preferable. But whether the harm to animals can actually be reduced depends not only on the scientific and technological means available, but also on the willingness of humans to recognise that an animal has in some (not necessarily overtly religious) sense an 'I' or 'thou', or is a 'subject of experience', qualifying it as having moral status. This thought adds an important dimension to the common Western approach and can contribute to the motivation of identifying and applying the Three Rs. In terms of the generally agreed need to minimise animal suffering, the classical Western and the non-Western approaches might therefore be considered as being morally complementary.

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28 Some regulations merely encode pre-existing good practice, such as the policy decision not to grant licences for research involving the great apes, which was implemented some years after the practice had ceased in the UK.

29 New applicants for personal licences are required to have successfully completed an accredited training programme comprising three or possibly four modules (with 'very limited exemptions'). The first module includes a section entitled *An introduction to ethical aspects of the use of animals in scientific procedures*. New applicants for project licences are required to have successfully completed a further module which includes a section entitled *Ethical aspects of the use of live animals*. See Home Office (1992) *Education and training of personnel under the Animals (Scientific Procedures) Act 1986*, available at: http://www.homeoffice.gov.uk/docs/training_statement1.html. Accessed on: 19 Apr 2005.

30 Clearly it is not possible to generalise from this example to a general paradigm of 'non-Western practice'. There is a wide spectrum of views, some of which are very close to what has been presented above as a 'Western' view. See, for example, Preece R (1999) *Animals and Nature: Cultural Myths, Cultural Realities* (Vancouver: University of British Columbia Press).

3.77 In summary, regulation may in some cases act as an emotional screen between researchers and animals, encouraging scientists (and others who handle animals) to believe that simply conforming to regulations is to act well. Yet, if the animal is regarded as having moral status, then the researcher should be made aware that to conduct experiments on another being without consent is morally problematic. It can be a matter of grave regret which in turn can prompt measures to reduce the need of using animals in this way rather than just because of regulatory requirements. Some form of regulation is accepted by practically all as *necessary* for good moral practice.[31] But it is important to be aware that it may not be sufficient.

## Summary

3.78 This chapter has aimed to lay out the critical elements of the current moral debate. We have argued that the following questions must be considered:

i) The debate is not best characterised in terms of the relative moral status of humans and animals but in terms of what features of humans and animals are of moral concern, in the sense of making certain forms of treatment morally problematic.

ii) Once those features are identified, the question needs to be asked as to how they should be taken into account in moral reasoning. Are they factors to be weighed against others, or do they function as absolute prohibitions?

iii) Finally, what does it mean to be a moral agent? How should moral agency be considered in the regulatory framework that governs animal research?

In general, we have not attempted to provide answers to these questions at this stage. We invite readers to reflect upon the discussion and examples provided in the following chapters in an unbiased way, and in the light of their own conclusions thus far. We present the conclusions of the Working Party in Chapters 14 and 15.

31 In addition to positively influencing moral agency, arguments in favour of regulation would be that it can (a) promote consistency; (b) enhance accountability; (c) act as a counter to commercial pressures; (d) reflect society's collective morality; and (e) promote legitimacy. We return to some of these elements in Chapters 14 and 15, see paragraphs 14.53–14.63, 15.14–15.15 and 15.53.

# Chapter 4

## The capacity of animals to experience pain, distress and suffering

# The capacity of animals to experience pain, distress and suffering

## Introduction

4.1 We have established that the question of the nature of any pain, suffering or distress that an animal might experience in scientific procedures is crucial when assessing the ethical implications of animal research. Many respondents to the Consultation also stressed the importance of taking animal welfare into account:

> 'The acceptability depends on the purpose and the amount of suffering for the animals.'
> *Professor Vera Baumans*

> 'Our ethical concerns should be geared to the animal's level of sentience.'
> *Dr Chris Jackson*

> '…there is little *real* effort to even begin to understand animal pain, distress and suffering, to identify what these terms describe or should describe… and then to address what we need to do to eliminate such states.'
> *Animal Research Issues Section of The Humane Society of the United States*

Determining whether sufficient efforts are being made to understand animal welfare is beyond the scope of this Report. However, we note that a number of organisations are already active in the field and have produced a considerable body of knowledge (see Box 2.4). In this chapter we summarise some of the important themes in the current debate about the capacity of animals to experience pain and suffering. We also address difficult conceptual and practical issues that arise when assessing the welfare of animals.

4.2 Common sense and empathy often appear to provide us with clear insight as to whether or not an animal is in a state of pain, suffering or distress. For example, even if we have not previously studied the behaviour of animals in a systematic way, it may be easy to assume that it is in great pain when it tries to escape, or when it makes sounds or facial expressions that are similar to those made by humans experiencing extreme pain. But these approaches have limitations, and it can be difficult to surmise what an animal is experiencing when observing more subtle behaviours. We may observe an animal's reactions to a stimulus, but are they indicative of pain as we understand the concept when we ascribe it to humans? And is it not more relevant to assess the welfare of laboratory animals in relation to the physiological and behavioural needs that are specific to the species, rather than trying to identify welfare states that are comparable to human pain and suffering? In this chapter, we explore these and other issues in more detail, seeking to address in particular the following questions:

- What is the biological function of pain, suffering and related states in animals and humans?
- Philosophically, and practically, can we ever assess with full certainty whether or not an animal is in a state of pain, suffering or distress? What are the scope and limitations of empathy, and objective scientific methods when assessing animal welfare?
- Can concepts such as pain, harm, distress and suffering, which are usually applied to humans, be applied in a meaningful way to all animals used for research? Are there some animals for which the identification of such states and the assessment of welfare are more difficult than for others?
- Which other aspects, apart from the experiment itself, need to be considered, when assessing the welfare of animals used in research?

### Box 4.1: Concepts relating to the assessment of welfare of animals

In discussing problems that arise when assessing the welfare of animals, we use the following terms, unless indicated otherwise:

- **Nociception**: The registration, transmission and processing of harmful stimuli by the nervous system.*
- **Pain**: 'An unpleasant sensory and emotional experience associated with actual or potential tissue damage'.†
- **Suffering**: 'A negative emotional state which derives from adverse physical, physiological and psychological circumstances, in accordance with the cognitive capacity of the species and of the individual being, and its life's experience.'‡
- **Distress**: Severe pain, sorrow or anguish.∫
- **'Pain, suffering, distress and lasting harm' in the Guidance on the Operation of the A(SP)A**: 'encompass any material disturbance to normal health (defined as the physical, mental and social well-being of the animal). They include disease, injury and physiological or psychological discomfort, whether immediately (such as at the time of an injection) or in the longer term (such as the consequences of the application of a carcinogen). Regulated procedures may be acts of commission (such as dosing or sampling) or of deliberate omission (such as withholding food or water).'
- **Sentient**: 'Having the power of perception by the senses'.** Usually taken to mean 'being conscious'.
- **Welfare/well-being**: These terms do not have sharp boundaries. The following statements are indicative of the ways in which they are commonly used:
  - Animals experience both positive and negative well-being. In assessing welfare, it is important to examine the animal's physiological and psychological well-being in relation to its cognitive capacity and its life experience.
  - Welfare is an animal's perspective on the net balance between positive (reward, satisfaction) and negative (acute stress) experiences of affective states.††
  - The welfare of any animal is dependent on the overall combination of various factors which contribute to both its physical and mental state. ‡‡
  - Welfare is the state of well-being brought about by meeting the physical, environmental, nutritional, behavioural and social needs of the animal or groups of animals under the care, supervision or influence of individuals.∫∫

* College of Medicine and Veterinary Medicine, University of Edinburgh *Guidelines for the recognition and assessment of animal pain*, available at: http://www.vet.ed.ac.uk/animalpain/Pages/glossary.htm. Accessed on: 11 Apr 2005.

† International Association for the Study of Pain (1994) *Pain Terminology* available at: http://www.iasp-pain.org/terms-p.html#Pain. Accessed on: 11 Apr 2005.

‡ Morton DB and Hau J (2002) Welfare assessment and humane endpoints, in *Handbook of Laboratory Animal Science: Essential principles and practices*, Vol I, 2nd Edition, Hau J and Van Hoosier GL (Editors) (Seattle, WA: CRC Press), Chapter 18, pp457–86.

∫ J Pearsall and B Trumble (Editors) (2003) *Oxford English Reference Dictionary* 2nd Edition (Oxford: Oxford University Press).

** J Pearsall and B Trumble (Editors) (2003) *Oxford English Reference Dictionary* 2nd Edition (Oxford: Oxford University Press).

†† Ethology & Welfare Centre, Faculty of Veterinary Medicine, Utrecht University (2004) *What we think*, available at: http://www.icwd.nl/think.html. Accessed on: 11 Apr 2005.

‡‡ Department for the Environment, Food and Rural Affairs (2004) *Animal Health and Welfare Strategy for Great Britain* (London: DEFRA), p16.

∫∫ Appleby MC and Hughes BO (Editors) (1997) *Animal Welfare* (Wallingford: CABI Publishing).

## Philosophical problems with regard to assessing the welfare of animals

4.3 Some people think that it is straightforward to interpret the dispositions of specific animals, as it often appears possible to 'read their minds'. It may seem especially easy in the case of primates such as the great apes, as they look most similar to humans. For example, some ethologists, who have studied the behaviour of animals in their natural habitat, argue that threat postures can be understood as mixtures of the human emotions of fear and aggression. Being familiar with these states, they take the view that it is possible to make accurate predictions from the postures about whether the animals are likely to escape or attack.[1] Another approach would be to draw on the human capacity for empathy, which we often use successfully when we judge dispositions or moods of other humans in specific situations. Since we would feel pain on being exposed to boiling water and would rapidly retract an exposed body part, it could seem reasonable to assume that an animal that shows a similar reaction on being exposed to boiling water would feel a similar kind of pain. Furthermore, many people believe that they 'understand' animals with which they have relatively close interactions in their everyday life, such as dogs or cats. By using familiarity,

1 Bateson P (1991) Assessment of pain in animals, *Anim Behav* **42**: 827–39.

empathy and methodological observation, many humans believe that they can assess accurately the dispositions and needs of animals. But sometimes these beliefs, however strongly held, may have little or no factual basis, and what appeared to be a self-evident truth may prove to have been an inappropriate ascription of a human form of behaviour or disposition, and a case of a simplistic *anthropomorphism*.

4.4 How can we verify that our observations match with the subjective experience of an animal? How can we get 'inside the mind' of an animal to be sure that behaviours which we perceive as signs of pain or suffering truly reflect these states? And how sure can we be that an animal which appears to be behaving normally is not in a state of pain or suffering? Philosophically, these and more general questions have been discussed under the title of *philosophy of mind*. The most radical and sceptical approach to assessing the dispositions of animals can be found in the 17th century philosophy of Descartes and Malebranche (see paragraphs 3.30 and 14.16). Based on a dualistic conception of mind and body, which in their view only applied to humans, they took the view that all animals were mere mechanistic automatons. Descartes, who had himself spent much time experimenting on animals, argued that animals lacked a *soul*, which, he believed, was required for higher cognitive capacities such as self-consciousness and the experience of pain and suffering. While animals were seen as capable of registering physical sensations, and reacting to them in different ways, Descartes suggested that the processes were not accompanied by conscious experience, claiming that animals which appeared to be in distress were really just 'mechanical robots [that] could give… a realistic illusion of agony'.[2] The philosophical and scientific bases for such views were later revised. Voltaire, commenting on his contemporary Descartes, observed: 'Answer me, machinist, has nature arranged all the means of feeling in this animal, so that it may not feel?' Many people found Voltaire's view more plausible. The acceptance over the past century of Darwin's theory that humans stand in an evolutionary continuum with other animals has further undermined the view that humans are in biological terms a radically distinct species, with exclusive capacities and dispositions (see paragraphs 4.8–4.10).

4.5 While, therefore, practically no serious contemporary philosopher argues that all animals are mere machines, there remains some scepticism about how reliably 'animal minds' can be read and understood. For example, even if familiarity, empathy and careful methodological observation are complemented by extensive recording of scientific evidence such as heart rate and hormonal and neural activity, the question remains as to whether it will ever be possible for humans to understand fully what it is like to be a particular animal, be it in a state of pain or even just in its normal state. This question is particularly relevant when we wish to ascertain the dispositions of animals that live in different environments to our own and possess different senses, such as the ability to hear ultrasound. In the words of the philosopher Thomas Nagel, who explored this question in some detail in a different context: will we ever be in a position to know 'what it is like to be a bat'? Is it not rather the case that we can only know what it is like for us to imagine to be a bat?[3]

4.6 For the purpose of the following discussion, we make several observations:

- First, a necessary condition for meaningfully describing states of pain, suffering and other dispositions in fellow humans appears to be that we are able to describe such states in ourselves. For example, we trust that the yawning which we observe in another human

2 Thomas D (2005) Laboratory animals and the art of empathy *J Med Ethics* **31**: 197–202.

3 See Nagel's article, 'What is it like to be a bat', for a more detailed philosophical discussion regarding the differences between first-person (experiential) data and third-person (quantifiable, scientific) data. Nagel T (1974) What is it like to be a bat *The Philos Rev* **83**: 435–50.

corresponds to a similar state of tiredness that we experience when we yawn in a comparable way.[4] Clearly, assessments made on this basis are more difficult if there are significant physiological and behavioural differences between the species being compared. Thus, it is not straightforward to claim that a primate, a cat or a snake that yawns feels tired in the same way that we might. While there is therefore some truth in the observation that we will never be able to know what it is like to experience the world from the point of view of a particular animal, such a requirement is mostly irrelevant with regard to assessing pain and suffering in laboratory animals. The fact that we will never be able to obtain proof of our hypotheses by getting 'inside the mind' of an animal does not prevent us from making the best possible approximations. Nagel's thought experiment therefore emphasises primarily the *reality* of subjectivity (i.e. it supports the view that it is plausible to assume that the way bats experience the world differs significantly from the ways beings that lack the capacity to perceive ultrasound experience it), rather than supporting the sceptical Cartesian view (see paragraph 4.4). By implication, it also enjoins us to compare animal welfare not exclusively to human dispositions, but to strive for alternative ways that may help to identify possible constraints on animal welfare, for example by considering their species-specific capacities and corresponding needs.

- Secondly, it is correct that humans will inevitably have to apply concepts such as pain, suffering and distress, which are used commonly and successfully in human-human interactions, when dealing with welfare assessments of animals. This means that care needs to be taken to avoid unwarranted anthropomorphism in using these terms.[5] Similar care in avoiding bias is required when making inferences based on familiarity, empathy and methodological observation.

4.7 In view of these observations, how are we to go about assessing welfare in other animals? We acknowledge that all welfare assessments of animals are imprecise and imperfect to a certain degree. However, we also take the view that meaningful assessments can be made. We therefore consider that the concept of *critical anthropomorphism* can be seen as a useful starting point. This approach involves the critical use of human experience to recognise and alleviate animal suffering by combining one's perception of a particular animal's situation with what can be determined by more objective, science-based observations.[6] We now examine in more detail whether such an approach can be successful.

## The evolutionary continuum

4.8 According to the accepted basic paradigm of evolutionary biology, there is a continuum from simple to more complex organisms. This ranges from primitive forms of life such as *Amoeba* and other single-celled and multicellular organisms to more complex forms, such as

4 It could be assumed here that, philosophically, the assessment of mental states in other humans is always straightforward, and that only animal states pose problems. However, this is not the case and there is intense debate about questions such as whether it will ever be possible for a person to know what another person's pain feels like, and whether they see the same hues of colours as we do. See, for example, Tye M (2003) *Qualia*, available at: http://plato.stanford.edu/entries/qualia/. Accessed on: 25 Apr 2005; Dennet D (1990) Quining Qualia, in *Mind and Cognition*, Lycan WC (Editor) (Oxford: Blackwell Publishers), pp519-48, available at: http://ase.tufts.edu/cogstud/papers/quinqual.htm. Accessed on: 25 Apr 2005. Thus, although we can generally make successful predictions about the mental states of other human beings it should not be forgotten that even such extrapolations may have their limitations.

5 In using terms such as pain or suffering, a wide spectrum of further connotations is often implied. In common-sense use, synonyms for suffering include affliction, distress, pain, agony, misery, torment, anguish, grief, sorrow, calamity, misfortune, trouble and adversity. When we say that someone suffers we also think of synonyms such as bear, abide, endure, lump, stand, stomach, swallow, take and tolerate. We use these terms primarily to describe states in ourselves and other humans. Care is required in applying them to animals, as it cannot be assumed that the terms always retain their meaning.

6 See Morton DB, Burghardt G and Smith JA (1990) Critical anthropomorphism, animal suffering and the ecological context *Hastings Center Report on Animals, Science and Ethics* **20**: 13–9.

vertebrates. Given what we know about how nervous impulses are transported and processed, it seems highly unlikely that animals without a nervous system, such as sponges, experience pain or suffering, but highly likely that animals with more complex anatomy and behaviour, including vertebrates, do.[7] Thus, primate species with higher levels of physiological, and especially neurophysiological, complexity have the potential to experience a given disease or procedure in a more similar way to humans.

4.9 Some people also emphasise the large number of genes that are shared between species. For example, humans share 99 percent of their DNA with chimpanzees and they argue that chimpanzees are therefore 'almost human'. But knowledge about the percentage of shared DNA has limited application in helping to decide whether or not an animal experiences pain and suffering in ways similar to humans. We also share significant amounts of DNA with animals with which we are less closely related, such as mice (96 percent) and fruit flies (70 percent), and indeed with crops such as bananas (50 percent). Furthermore, the same gene may be expressed in different ways, or for different periods, or interact in different ways with other genes, which means that having genes in common is information that is of limited relevance with respect to assessing welfare.[8]

4.10 Clearly, however, evolutionary continuities in the form of behavioural, anatomical, physiological, neurological, biochemical and pharmacological similarities provide sufficient grounds for the hypothesis that those animals that possess relevant features are capable of experiencing pain, suffering and distress.[9] Evolutionary continuity also means that, on scientific grounds, animals can, in specific cases, be useful models to study human diseases, and to examine the effects of therapeutic and other interventions. Nevertheless, the question remains as to what exactly evolutionary continuity means with regard to the *quality* of pain and suffering which animals are capable of experiencing. If we use animals as models for diseases that are painful for humans, such as neuropathy, is it not reasonable to expect that the animal models will experience similar pain? We note that for animals to provide valid models, it is usually only important that some element of their bodily processes should be similar to that of humans (see Chapters 5–9).[10] They do not always need to show *all* the typical signs of a disease, but just those relevant to a specific research question. Arguments claiming that all animals used as models for human diseases necessarily suffer '…assume that all the systems involved in the detection of pain evolved as a unitary package, which is either present and works in its entirety or is absent and does not work at all… this assumption is not merely implausible, it is wrong. Most complex neural functions can be dissociated into sub-systems and, even in humans, parts of the pain system can be intact while others are deficient. Furthermore, it remains far from obvious that all animals that

7 See also Chapter 4, footnote 27.

8 The percentage of genes that are shared between two species is not very informative. See, for example, Oxnard C (2004) Brain evolution: mammals, primates, chimpanzees, and humans *Int J Primatol* **25**: 1127–58. Individual genes can code for more than one protein through alternative splicing. They can also be expressed in a variety of different ways depending on how they are regulated. In addition, a significant proportion of the genome is not in the form of genes and is referred to as 'junk DNA'. Its functions are thought to be involved in genetic regulation. It is also noteworthy that changes in a single gene alone can be dramatic. For example, chimpanzees and humans became divided from a common ancestor at least five million years ago. About 2.4 million years ago, an important gene mutation occurred in the line that developed into the human species. It has been shown that this mutation resulted in a reduction of the size of the jaw muscles, and may have allowed the brain to expand and develop into its modern human form. See Stedman HH, Kozyak BW, Nelson A *et al*. (2004) Myosin gene mutation correlates with anatomical changes in the human lineage *Nature* **428**: 415–8.

9 See, for example, Bekoff M (2002) *Minding Animals: Awareness, Emotions and Heart* (Oxford and New York: Oxford University Press); Goodall J and Bekoff M (2002) *The Ten Trusts: What We Must Do to Care For the Animals We Love* (San Francisco: HarperCollins); Panksepp J (2003) 'Laughing' rats and the evolutionary antecedents of human joy? *Physiol Behav* **79**: 533–47.

10 For example, although humans and mice clearly differ in their appearance, the function of anatomical structures such as tendons is the same in both, and results from studies on tendons in mice can readily be transferred to humans.

escape from and avoid damage to their bodies have reflective consciousness.'[11] We now discuss in more detail significant biological differences between humans and animals, and differences between kinds of animals. We focus on physiological and neurological development, and describe their importance for welfare assessments.

## Pain, suffering and distress: meaning and function in animals and humans

### *The basic evolutionary functions of pain and ways of relieving it*

4.11 In evolutionary terms, pain has evolved from nociception as an aversive sensory mechanism that warns of harmful experiences. Pain has three main functions: First, it allows animals and humans to avoid dangerous situations, as painful experiences usually prompt an immediate impulse to withdraw and escape from situations that cause harm, usually in the form of tissue damage. Secondly, as pain is associated closely with the environmental context in which it occurred, its experience can help to prevent repeated damage. Pain-causing experiences will be avoided through learning when a similar environment is encountered again. Thirdly, pain promotes the healing of injuries, as affected body parts are not used in normal activities, as far as possible.

4.12 In the natural environment where there are predators, and competition for mates and food, an overt display of pain-related behaviour could be disadvantageous. For example, an animal showing obvious signs of pain such as lameness or pain-related vocalisation could become a target for predation or aggression which would reduce its chances of mating or survival. Due to evolutionary pressures, many animals have therefore developed mechanisms that suppress signs of acute and chronic pain resulting, perhaps, from injury or an attack. Animals, including humans, produce opioids (natural 'painkillers') which may remain effective for a few minutes or several hours.[12] These internally secreted opioids are released when chronic pain increases. This occurs through higher levels of activity of the ascending chronic pain pathways of humans and other animals (Figure 4.1). They trigger pain-suppressive pathways (known as descending pathways) which originate in the brain stem. This knowledge has been used to develop means for the alleviation of pain in animals and humans by administering the opiate morphine, which acts on the same receptors. The sensation of pain can sometimes be partly or completely blocked by these natural endogenous pain relieving chemicals which are a physiological response to injury.

4.13 It is also important to note that the capacity for, and nature of, suffering probably depends on specific selection pressures which have acted on different species, favouring certain brain structures and functions over others. This phenomenon can be illustrated by considering the loss of an offspring. In humans, the suffering and distress from the loss of a child is emotionally devastating and debilitating, feelings that may persist for many years, even throughout life. Other species show signs that indicate severe distress at the loss of an infant, such as carrying the body around for several days.[13] Rodents, which mate more frequently and produce larger litters, do not display similar behaviours. Even if a whole litter of infants is removed, they return within hours to oestrus and mate again.

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11 Bateson P (1991) Assessment of pain in animals *Anim Behav* **42**: 827–39.

12 Lohmann AB and Welch SP (1999) ATP-gated $K^+$ channel openers enhance opioid antinociception: indirect evidence for the release of endogenous opioid peptides *Eur J Pharmacol* **385**: 119–27.

13 Some animals display the characteristic behaviour we associate with grief, such as withdrawal from the group or loss of appetite. For example, sea lion mothers, watching their infants being eaten by killer whales, squeal and wail. Some animals try to revive the corpse or carry it around until it decomposes. Primatologist Jane Goodall observed an eight year old male chimpanzee withdraw from its group, stop feeding and eventually die following the death of his mother. See Bekoff M (2000) Beastly passions *New Scientist* 29 April.

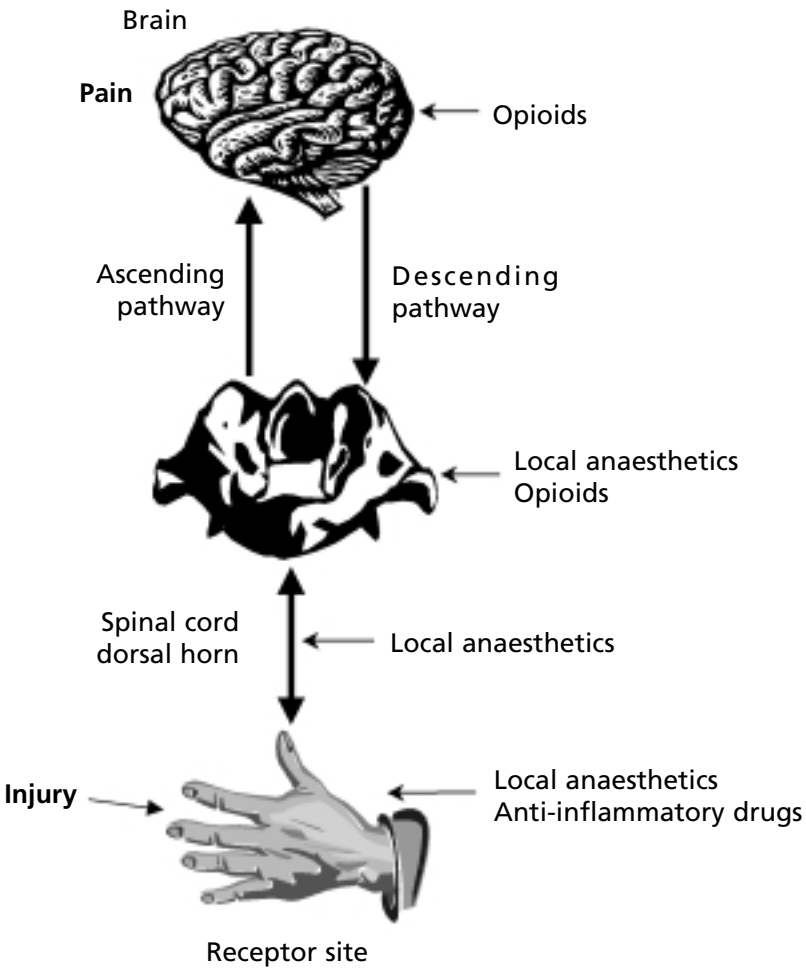


**Figure 4.1. The pain pathway and interventions that can modulate activity at each point**

Opioids bind to opioid signal receptors in the central nervous system, affecting the descending pain pathway in the brain and the spinal cord.*

* Gottschalk A and Smith DS (2001) New concepts in acute pain therapy: preemptive analgesia *American Family Physician* **63** (10). Redrawn with permission from Kehlet H and Dahl JB (1993) The value of 'multimodal' or 'balanced analgesia' in postoperative pain treatment *Anesth Analg* **77**: 1049.

4.14 Of course, the fact that an animal rapidly returns to mating condition cannot automatically be taken as evidence that it did not experience any form of suffering. Such questions might be elucidated by empirical research into levels of stress indicators. However, it could be hypothesised that evolutionary mechanisms might have favoured the capacity for experiencing relatively greater suffering in the case of infant loss in those species that breed infrequently and produce few offspring. Each infant represents a significant investment of time and resources and therefore individual animals that are motivated to take more care of their offspring are more likely to pass on their genes.

***Representations of pain and suffering and their neurological context***

4.15 In most mammals, the ascending pain pathways not only relay nervous impulses in the brain stem, but also in the thalamus before ascending to the somatosensory or 'touch' neocortex, which enables the localisation of pain. In humans, this localisation can be exceptionally

accurate for *primary* pain, which can result, for example, from a knife cut or burn, but inaccurate for chronic deep-organ pain because there is no mapped representation of these areas in the human brain.[14]

4.16 Pain pathways also extend to other areas of the cortex, known as the association cortex, the great expansion of which is unique to humans and certain other primates, such as the great apes. These areas are virtually non-existent in the brains of rodents, where more than 70 percent of the cortical structures are responsible for processing olfactory information (in humans, less than one percent of cortical structures have this function). It is significant that the embeddedness of pain processing in the association cortex in humans contributes to the emotional dimension of pain, which is a characteristic of suffering. It is therefore possible to interpret suffering as a higher-order phenomenon in that it relates to the experience of chronic pain in a predominantly negative way. Furthermore, this finding suggests that animals such as mice, which lack similarly developed brain structures, may be very unlikely to experience suffering resulting from pain in a similar way, although they do suffer pain itself. Therefore, evidence about differences in the way in which pain is embedded in the brains of different animals supports the view that care is required when ascribing states such as suffering to mice.

4.17 The embeddedness of pain processing in the association cortex also appears to contribute to the phenomenon that suffering can be extremely variable between, and within, individuals. Some humans, and possibly also some closely related animals, have the ability to feel pain and suffering when there is no pain stimulus, to be untroubled by pain when there is what others would objectively describe as pain and even to enjoy pain being inflicted in sexual contexts. In adults, the fear of the dentist can intensify innocuous sensations, but the belief that it is a price worth paying in order to avoid far greater suffering can also render the experience of the treatment less significant. The latter capacity is not usually found in children, which may suggest that beings with less developed rational capacities are not necessarily suffering less, but more, since they are not in a position to conceptualise the pain as a means to an end.

## Subjective and objective elements of assessing welfare: a correlative approach

4.18 How, in practice, is it possible to assess whether or not animals experience pain, suffering or distress? And how far can our assessments be free from anthropomorphisms? Below we consider four approaches:[15]

(i) evaluation of clinical signs;

(ii) study of animals' choices;

(iii) familiarity with ethological and ecological data; and

(iv) consideration of physiological and neurological features.

In discussing each approach, we also aim to assess how far the criteria used are likely to be biased by unjustified ascription of human dispositions to animals, thus analysing further the feasibility of the concept of critical anthropomorphism (see paragraph 4.7).

14 Primary pain is conducted exceptionally quickly, resulting in rapid withdrawal of affected body parts where possible. By contrast, pain brought about by tissue damage of internal organs is usually conducted more slowly, resulting in chronic, intense suffering. However, there are also exceptions to this pattern, since colic causes a very acute pain, and bone metastases can cause twinges of substantial pain.

15 All four approaches come into play when defining good practice for assessing welfare, although specific categories may receive more attention than others. Since this chapter addresses the question of how to assess pain, suffering and distress in animals from first principles, and since there is considerable overlap between approaches (i)–(iv), we discuss them under one heading.

### *Evaluation of clinical signs*

4.19 Clinical signs of adverse effects on welfare take a wide range of forms. At one end of the spectrum, animals may seek vigorously and repeatedly to escape from cages, or they may resist vehemently being handled in certain ways. There are other, less obvious signs, such as changes in biological features including food and water consumption, body weight, levels of hormones and glucose, adrenal gland mass, or species-specific appearance, posture and behaviour.[16] Measures of these changes are generally used in conjunction with one another to provide a basis for assessing stress, since, for example, elevated levels in the blood of a hormone called cortisol (a 'stress hormone') is a reliable indicator of stress as well as a response to more positive circumstances.

4.20 Clinical signs such as body weight and temperature, respiration and heart rates can be measured in objective ways. Others, such as the quality of respiration (deep, shallow, laboured), posture, appearance (closed eyes, ruffled coats, fur or feathers), diarrhoea, coughing and convulsions are more difficult to quantify. Nonetheless, in veterinary clinical practice, it is possible to grade them in a standardised way. For example, an animal may be 'hopping lame', or bear some weight and be limping. More formal and defined assessments of clinical signs, normal behaviours and particularly abnormal behaviours also enable more objective measurements of pain and suffering.

4.21 Trained personnel can gain a significant amount of information about an animal's well-being through evaluation of a set of clinical observations.[17] These include measurement of physiological parameters relevant to the species and situation, and awareness of the animal's behavioural responses to pain and suffering. While valid and verifiable quantifiable data are necessary for making reliable welfare assessments, they are not sufficient. No single sign, whether seen as subjective or objective, can directly inform a researcher, veterinarian or animal technician about the general disposition of an animal. A number of different parameters need to be integrated with the more subjective observations to achieve a meaningful evaluation.

### *Study of animals' choices*

4.22 Another useful way of assessing whether or not specific situations are subjectively unpleasant for animals is to measure animals' choices. An approach initially proposed by Marian Dawkins, tests animals' preferences between a given set of options and their motivation to gain access to resources (see Box 4.2).[18] While the approach clearly does not bring us any further in getting 'inside the mind' of the animals in the philosophical sense (paragraphs 4.4 and 4.6), it can be very useful for understanding species-specific needs while avoiding anthropomorphisms (see paragraph 4.3). Testing animals' choices can allow researchers to select from a range of possible housing conditions those that are preferred by the animals, thus providing them with resources that they value.

16 See Moberg G and Mench JA (Editors) (2000) *The Biology of Animal Stress, Basic principles and implications for animal welfare* (Wallingford: CABI Publishing).

17 See Rutherford M (2002) Assessing pain in animals *Anim Welfare* **11**: 31–53; Paul-Murphy J, Ludders JW, Robertson SA *et al*. (2004) The need for a cross-species approach to the study of pain in animals *J Am Vet Med Assoc* **224**: 692–7; Bateson P (1991) Assessment of pain in animals *Anim Behav* **42**: 827–39.

18 Dawkins MS (1980) *Animal Suffering: The Science of Animal Welfare* (London: Chapman and Hall).

### Box 4.2: Choice and avoidance tests and economic demand theory

***Choice and avoidance tests***

Researchers have designed experiments to measure the choices and avoidances of animals in different situations or environments, and when presented with different stimuli. This kind of research is sometimes carried out to increase knowledge about the species-specific basic behavioural dispositions of particular animals in standardised situations. The experiments may also be used to try to assess, for example, the appropriateness of different cage designs, the provision of enrichments, or to measure the effect of a pharmaceutical intervention on the behaviour of animals that are suffering from a given disease.

A choice and avoidance test might be designed to identify which type of bedding a laboratory animal would prefer. Various materials would be provided to see which is chosen by the animals. Alternatively, a cage comprising two parts could be designed, each with different bedding materials. Animals placed in the cage would then be observed as they make their selection. Choice and avoidance tests have also been designed to test whether animals find certain circumstances or procedures painful. For example, rats have been provided with solutions containing either sugar or pain relieving medicines in their normal laboratory state and when experiencing a condition that would be expected to be painful. Experiments show that healthy rats choose to drink the sugar solution whereas rats with inflamed joints prefer to drink the solution containing an analgesic.*

***Tests of economic demand theory***

Dawkins developed further choice tests by drawing on the idea of *inelastic* and *elastic* demands, which are commonly used in economics.† According to this theory, the demand for a reward will be influenced by price. This type of test can be used to assess whether an animal will escape from what may be an adverse experience irrespective of the cost of escaping. For an animal the cost might be discomfort, pain or an inferior choice of food. Conversely, a beneficial situation can become more or less desirable depending on the costs to the animal. For example, during experiments in which researchers administered an injection that caused some discomfort to rats after they ate a particular food, it was found that the rats did not subsequently choose this food item; they learnt not to choose the short-term benefit.‡ In other experiments, rats have shown a preference for a solid floor over a metal grid floor and the strength of that preference has been investigated. Rats were given a choice of sleeping on a grid floor or lifting a weighed door to obtain access to a solid floor with sawdust bedding. Only when the weight increased to near that of the rats' own bodyweight did the animals stop trying to access the solid floor. Thus it could be concluded that solid floors are highly important to the behavioural needs of rats.∫

* Colpaert FC, De Witte P, Maroli AN *et al*. (1980) Self-administration of the analgesic suprofen in arthritic rats: evidence of *Mycobacterium butyricum*-induced arthritis as an experimental model of chronic pain *Life Sci* **27**: 921–8.

† Dawkins MS (1990) From an animal's point of view: motivation, fitness and animal welfare *Behav Brain Sci* **13**: 1–61.

‡ See Bateson P (1991) Assessment of pain in animals *Anim Behav* **42**: 827–39.

∫ Manser CE, Elliott HE, Morris TH and Broom DM (1996) The use of a novel operant test to determine the strength of preference for flooring in laboratory rats *Lab Anim* **30**: 1–6.

### *Ethological and ecological data*

4.23 We said above that suffering can be defined as:

> 'a negative emotional state which derives from adverse physical, physiological and psychological circumstances, in accordance with the cognitive capacity of the species and of the individual being, and its life's experience.'

In the second part of the sentence, the definition refers to the welfare 'of the species and of the individual', which raises issues that require further discussion. The two previous approaches focused on monitoring of clinical signs and the choices of individual animals kept in laboratory environments. To assess well-being more comprehensively, it is also important to be familiar with the way in which particular species behave in their natural environment.

4.24 Ethology is the scientific study of animal behaviour. A range of different ways of quantifying, measuring and documenting animal behaviour have been developed. Animal ecology refers to the scientific study of the relations of organisms to one other and to their physical surroundings. Both fields of study make useful contributions to the assessment of animal welfare. First, they can help to identify suitable (and unsuitable) environments in which animals might be kept under laboratory conditions. Secondly, awareness of an animal's natural behaviour can be useful to identify states of well-being or stress (see paragraph 4.22).

4.25 However, as we have said (paragraphs 3.41–3.43), there is disagreement about the importance of comparisons with an animal's natural environment. Defining a natural environment is not straightforward. For example, mice and rats not only live in natural

habitats such as forests or meadows, but also in urban environments. These animals are highly adaptable and this ability may bring into question the need for the study of behaviour in their 'natural' habitats. In addition, nearly all of the laboratory animals used in research in the UK have been bred for the purpose.[19] Some researchers therefore argue that the behaviour of these animals in natural environments is simply not relevant, and that they will not miss any features that they have not known in the laboratory environment.

4.26 These arguments are problematic. For example, it was recently reported that laboratory-bred rats can rapidly adapt to a more natural environment when released into a large outdoor enclosure. The rats were able to perform behaviours that the laboratory environment prevents, for example, digging and climbing (see paragraphs 4.37–4.42).[20] Furthermore, while many animals can live in a range of different environments, there are also limits to their ability to adapt. Unsuitable environments may cause stress because most animals will seek to exhibit intrinsic behaviours. If the environmental constraints are very strong, animals may fail to adapt and even die. If the constraints are less severe, they may still cause stress that may be evidence by stereotypic behaviour (Box 4.3). For example, it would not be desirable to confine dogs, which are members of a roaming species, to very small pens. Similarly, primates and rats are social animals and, in their natural environment, live in groups. Keeping them in compatible, stable groups is therefore preferable to keeping them housed singly.[21] It is also important to most animals that they are allowed to forage for food, rather than obtaining it from a bowl or dispenser. Familiarity with species-specific needs can therefore allow people who handle and work with laboratory animals to assess more easily whether environments are likely to constrain or support the welfare of individual animals.

### Box 4.3: Stereotypic behaviours

Some animals in captivity exhibit 'stereotypic behaviours'. These are defined as repetitive, unvarying behaviours that appear to have no goal or function, such as recurring and excessive gnawing, pacing, circling or jumping. Animals tend to develop stereotypies as a result of an inadequate environment, stress, frustration or a reduction in social interactions.*

* Rodent Refinement Working Party (1998) Refining rodent husbandry: the mouse *Lab Anim* **32**: 233–59.

***Consideration of physiological and neurological features***

4.27 We are familiar with the consequences of manipulating pain pathways in ourselves through subjective experience and methodological inquiry. It is therefore reasonable to assume that animals with very similar physiological structures experience similar states of pain, suffering and distress (paragraphs 4.16–4.17). But assessments become more difficult for animals that are less similar to humans, particularly if they live in different environments. Evolution has produced a range of adaptive solutions to environmental challenges. For example, flight has been resolved in several different ways in insects, bats and birds. Similarly, it is plausible to assume that the principal function of pain as a 'special-purpose damage-avoidance system' has been realised in a variety of ways across different species.[22] For example, insects such as the fruit fly have pain receptors but no nervous system equivalent to the pain pathways in mammals.[23] Nonetheless they have complex nervous systems that enable them

19 Most animals used in research in the UK, except farm animals, must only be obtained from designated breeding or supplying establishments (see paragraph 13.24).

20 *The Laboratory Rat: A Natural History*, available at: http://www.ratlife.org/. Accessed on: 20 Apr 2005.

21 Note that the use of wild-caught primates is banned in the UK under the A(SP)A, except where exceptionally and specifically justified.

22 Bateson P (1991) Assessment of pain in animals *Anim Behav* **42**: 827–39.

23 However, there is evidence that some insects likely experience pain. See Bekoff M (Editor) *Encyclopedia of Animal Rights and Animal Welfare* (Westport: Greenwood Publishing Group); Bekoff M (Editor) *The Smile of a Dolphin: Remarkable Accounts of Animal Emotions* (Washington, DC.: Random House/Discovery Books).

to associate odours with electrical shocks, prompting them to avoid such odours on subsequent occasions.[24] Similarly, the common octopus (*Octopus vulgaris*), which was included in the A(SP)A in 1993, does not have similar neurological pathways to humans, but is able to associate visual and tactile stimuli with electrical shocks.[25] The octopus also possesses chemoreceptors that allow the detection of substances at very low concentrations.[26]

4.28 Empirical research has sought to assess the functioning of nervous systems in such animals and to determine whether they are capable of experiencing pain or suffering in ways to which we can relate. At the same time, the fact that humans and some other animals possess nociceptors and a system of neural pathways does not in itself prove that there are no other ways of producing conscious experience. While physiological and neurological analogies in animals may therefore be useful indicators of comparable experiences, the absence of analogous structures cannot necessarily be taken to mean that they are incapable of experiencing pain, suffering or distress or any other higher-order states of conscious experience.[27]

## Summary of paragraphs 4.3–4.28

4.29 In conclusion, it is extremely difficult to determine *exactly* the subjective experiences of animals in relation to pain and suffering. However, the evolutionary continuum that is obvious from physiological, neurological and behavioural similarities between humans, primates and other animals allows us to make meaningful *approximations*. While we need to ensure that applying terms such as pain and suffering to animals does not lead to undue anthropomorphism, their vagueness does not render them inapplicable or useless. It is also important to consider the fact that animals may experience negative welfare from circumstances that would not be sources of harm for humans. Awareness of behavioural and physiological species-specific needs to identify and assess deviations from that state is therefore essential. While assessment of animals' behavioural and physiological responses to resources and environmental conditions is primarily a matter of empirical research and relatively straightforward, interpretation of the welfare implications for laboratory environments can be more complicated.

4.30 In the spirit of *critical anthropomorphism*, a combination of the evaluation of clinical signs, the study of animal choices, familiarity with ethological and ecological data, and consideration of physiological and neurological features can all allow for useful predictions of animals' requirements and assessments of well-being, based on sound scientific evidence

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24 Dudai Y, Jan YN, Byers D *et al*. (1976) A mutant of Drosophila deficient in learning *Proc Natl Acad Sci USA* **73**: 1684–8.

25 The Animal Procedure Committee (APC) recommended that the common octopus be brought into the A(SP)A in 1992. The Animals (Scientific Procedures) Act (Amendment) Order (1993) brought this change into effect. In 2001, the Committee recommended that all cephalopods should be included in the Act as the addition of only one species, *Octopus vulgaris*, appeared to be anomalous. See APC (2002) *Minutes from APC meeting*, February 2002, available at: http://www.apc.gov.uk/reference/feb02.htm. Accessed on: 26 Oct 2004. As yet, no other invertebrate species have been included in the A(SP)A.

26 See APC (2002) *Minutes from APC meeting*, February 2002, available at: http://www.apc.gov.uk/reference/feb02.htm. Accessed on: 26 Oct 2004. For further information see Hanlon RT and Messenger JB (1996) *Cephalopod Behaviour* (Cambridge: Cambridge University Press).

27 Note that it would be fallacious to infer from this argument about the *possibility* of conscious experience in animals with very different neurological and physiological features, that there *must be* a range of animals which certainly possess such experiences. On the basis of an ethical 'precautionary approach' it might be tempting to err on the safe side and assume that this is the case. However, a representationalist and functional analysis of conscious experience shows that, among other things, beings capable of conscious suffering would require an integrated self-model (in order to develop a sense of ownership for the represented pain, fear or distress), representation of time (in order to possess a psychological moment, an experimental 'now'), working memory and most probably the capacity for emotions (in order to represent negative value, at least in an non-conceptual manner). See Metzinger T (2003) *Being No One – The self-model theory of subjectivity* (Boston: MIT), Chapter 3.

and processes. In this context, two respondents to the Consultation commented as follows:

> 'It may well be that we can make significant improvements to the well-being of lab animals by making relatively simple modifications to standard husbandry practice. However, it is important not to be too anthropomorphic about what we conceive as quality of life for other animals, and what we do should be informed by more research into animal behaviour and cognition.'
> *Professor Julian Blow*

> 'Many schemes are available for scoring welfare and/or suffering in laboratory animals, and they can undoubtedly be useful. However, what is really needed is a commonsense approach. Nobody who has lived with dogs and cats can fail to know when they are suffering, whether or not we could quantify it or describe it perfectly. We must not let those who want to apply experimental procedures to animals get away with clever and pseudoscientific arguments about animal consciousness, ability to perceive pain, etc., as a means of escaping the need to justify what they want to do.'
> *Professor Michael Balls, Chairman of the FRAME Trustees*

We conclude that judgements based on scientific evidence, and those based on empathy must be taken into consideration in assessments of animal welfare. Undue anthropomorphism, and the viewing of animals as mere research tools are equally inappropriate. We return to the ethical arguments about animal research in Chapters 14 and 15 and now consider more specific aspects relating to possible sources of suffering of laboratory animals.

## Sources of harm for laboratory animals

4.31 The discussion about pain, suffering and distress that research animals may experience is often focused on experimental procedures. Respondents to the Consultation also pointed out that:

> 'It is not only scientific procedures that can cause suffering to animals, but also the conditions of their captivity. Many laboratory animals are kept in bare, sterile living conditions…'
> *The Dr Hadwen Trust for Humane Research*

> 'Environmental factors…have a great impact on the laboratory animal throughout its entire life, not only during experiments.'
> *Professor Vera Baumans*

Animals may experience adverse physiological and psychological states that can result from a range of factors (Box 4.4). We now give systematic consideration to a number of areas that influence an animal's welfare independent of, or in addition to, specific experimental procedures. These include:

- breeding (including the use of wild-caught animals);
- transportation;
- housing;
- husbandry and care;
- handling;
- restraint;
- identification;
- any adverse effects of the procedures (e.g. nausea from toxic compounds, discomfort and pain from induced syndromes, natural and experimental infections); and
- euthanasia.

As this list demonstrates, the full lifetime experience of animals involved in research must be carefully considered and given due weight to permit an adequate evaluation of the harms or 'costs' that are likely to arise. Such evaluations always need to be specific to the context. As will be clear from the discussions in Chapters 5–9, animal research takes a wide range of forms and the implications for welfare depend significantly on the type of research. There is also variation in two other important factors. First, although there are a number of codes of practice that set out minimum standards, for example for the size of cages (see paragraph 13.10), facilities often vary with regard to providing conditions above the minimum standards. Secondly, whether or not animals will experience pain and suffering also depends critically on the skills and motivation of those handling them to implement Refinements, such as the use of pain relieving medicines or the provision of enrichments (see Chapter 12). We therefore do not attempt to describe the full range of welfare implications that *all* animals will necessarily experience when used in research. Rather, we aim to provide a systematic description of the types of effects that animals *may* experience, depending on the circumstances in which they are used.[28] Many of these effects can be lessened considerably by best practice in animal care and welfare, and responsible scientists and animal technicians will seek to reduce them as far as possible.

### Box 4.4: Adverse physiological and psychological states

Animals can experience both physiological and psychological adverse states. These are intimately linked and dependent upon one another, as the physiological and behavioural response to stress affects a number of biological functions and systems. For example, animals housed at artificially low temperatures will be under physiological stress as they expend energy to maintain their core body temperature by huddling together, shivering and reducing the blood supply to the skin. If such stress is extreme or prolonged, substantial effort will be required to maintain a state of equilibrium. The animals may become aware of this effort and suffer as a result.

Alternatively, a social animal housed individually in a barren cage at an appropriate temperature, relative humidity and light level may not be under any immediate physiological stress but will probably experience psychological stress due to boredom and anxiety. This can lead to physiological changes such as alterations in heart rate and body temperature, and disturbed sleep patterns.*

* Späni D, Arras M, König B and Rülicke T (2003) Higher heart rate of laboratory mice housed individually vs in pairs *Lab Anim* **37**: 54–62.

***Breeding***

4.32 The process of breeding animals for laboratory use can involve the thwarting of many natural behaviours. Most significantly, laboratory animals are usually weaned and separated from their mothers at a time convenient for research purposes, which rarely coincides with the time when they would have dispersed naturally. It is sometimes argued that this is not a problem since some animals 'drive' their offspring away in any case. However, in many species, the separation is not total and permanent; the young join the extended colony and kin relationships are maintained. Early weaning can thus be stressful for both the juvenile animals and their mothers.[29] This feature is increasingly recognised in primates, and it also needs to be considered in the case of other animals that care for their young.

4.33 Another important aspect of breeding concerns the possibility of wastage of newborn animals which are euthanised because they are surplus to requirements. Such wastage can sometimes arise if there is lack of communication and forward planning, or if only one sex is required. Care also needs to be taken that standards of housing and care for breeding animals are of similar quality to those which should be provided for research animals.

28 Further information on adverse effects and on ways of preventing or alleviating them can be found in a series of reports by the BVAAWF/FRAME/RSPCA/UFAW Joint Working Group on Refinement, which cover husbandry and care; the administration of substances and GM mice.

29 Kanari K, Kikusui T, Takeuchi Y and Mori Y (2005) Multidimensional structure of anxiety-related behavior in early-weaned rats *Behav Brain Res* **156**: 45–52.

### *Use of wild-caught animals*

4.34 Most laboratory animals are bred specifically for the purpose, but some are caught from the wild, especially for use in basic biological research. For example, some wild birds are caught for physiological studies; many *Xenopus* frogs are caught in the wild and some countries still use wild-caught primates (although not the UK) or obtain captive-bred primates from breeders who replenish their breeding stock with animals captured from the wild. In the UK, the use of wild-caught primates is prohibited except where exceptional and specific justification can be established (see paragraph 4.26).

4.35 Capture from the wild imposes significant psychological stress on animals that are not habituated to humans or to captivity. It usually presents a number of risks to the animal and can result in physical injury, shock or even death. In addition to the impact on the target animal, effects on other animals also need to be considered as they may experience stress leading to behavioural disturbances that could leave them open to predation or cause them to abandon their young. This could affect not only other members of the colony in social species, but also animals of other species that are disturbed during the capture process.[30]

### *Transport*

4.36 Transport is a significant life event for laboratory animals and it may involve a number of aversive and stressful elements.[31] Studies of animal transport have focused primarily on farm rather than laboratory animals.[32] It has been hypothesised that stressful conditions could affect both the welfare of laboratory animals and the scientific validity of any future studies involving the animals or their offspring. The precise effect of transport varies depending on transit time, the species involved and a number of more detailed circumstances. The implications of transportation over short distances, such as moving mice within a building, as well as that over longer distances, as in the case of the import of macaques from their country of origin to the UK, which can take up to 60 hours, need to be considered.[33] Adverse effects from transport can result from factors that include the following:

- handling (see paragraphs 4.44–4.47);
- separation from familiar animals;
- housing changes;
- confinement in an unfamiliar transport container;
- loading and unloading, movement and vibrations during the journey, including acceleration and deceleration;
- physical stress due to maintaining balance (especially for larger animals);
- unfamiliar sights, sounds and smells;
- fluctuations in temperature and humidity;
- availability of food and drinking water; and
- disruption of light/dark regimes and possibly adaptation to a different time zone.

30 Implications of any authorised *release* to the wild also need to be considered. The A(SP)A states that 'Where a project licence authorises the setting free of a protected animal in the course of a series of regulated procedures, that licence shall include a condition requiring the prior consent of the Secretary of State to the setting free of the animal.' See A(SP)A Section 10 (3B).

31 See Swallow J, Anderson D, Buckwell AC *et al*. (2005) Report of the Transport Working Group established by the LASA: Guidance on the transport of laboratory animals *Lab anim* **39**: 1–39.

32 See Grandin T (1997) Assessment of Stress During Handling and Transport *J Anim Sci* **75**: 249–57.

33 See Tuli JS, Smith JA and Morton DB (1995) Stress measurements in mice after transportation *Lab Anim* **29**: 132–8.

Stress during longer journeys may also increase the risk of disease for transported animals. The potential to monitor animal well-being, and to act if it is compromised, is often significantly curtailed during such transport.

***Housing***

4.37 Breeding, stock and experimental animals spend most of their lives in cages or pens, not actually undergoing procedures. The size and quality of the housing environment therefore has a highly significant impact on their well-being. Current knowledge of animal behaviour and welfare makes clear that captive animals need adequate space for a range of natural behaviours including: appropriate social behaviour, exercise, foraging and play, solid floors of appropriate material and group housing for social species.

4.38 Where animals are housed in small and barren cages, they cannot perform their full range of species-specific behaviours. Housing conditions may thus prevent certain social behaviours such as the maintenance of appropriate distances between individuals. Research has demonstrated that inadequate environments have been the direct cause of a range of adverse physiological and psychological effects, for example the increased likelihood of active animals to suffer from osteoporosis when they are kept in small cages. Many animals, especially dogs, experience welfare improvements when enrichments such as refuges or viewing platforms are provided, which can assist in their perception of an environment as 'secure'. Not providing for these needs can cause stress to the animals.

4.39 In their natural environment, all of the commonly used laboratory rodents, apart from guinea pigs, will dig tunnels or chambers in order to create refuges. Even animals from inbred strains will create such structures, which can be highly complex, if they are given the opportunity to do so. However, usually, few if any laboratory rodents have the opportunity to burrow and some experimental protocols may require animals to be kept in environments without enrichments such as artificial tunnels or refuges.

4.40 Some species, such as rats, experience better welfare if nesting material is provided. For example, female rats housed without a refuge will nurse their pups in the 'cover' position in an attempt to protect them, rather than the 'half-moon' position of a more 'relaxed' mother rat that feels safe within her nest. Nesting material is not only important for nursing mother rats. Its availability improves welfare for both sexes and throughout all stages of life.[34]

4.41 The type of food, and the way it is presented, also influences animal well-being. In their natural environment, most rodents are omnivores and visit many different feeding sites in a day whereas laboratory rodents are generally fed on standardised diets from fixed food dispensers. Many animals are highly motivated to explore relatively large areas and to forage even when food is freely available, a phenomenon known as *contrafreeloading*. It has been suggested that evolutionary pressures have led to animals being adapted to contrafreeload in order to find out more about their environment, helping them to prepare for possible food shortages. Thus thwarting such behaviour by housing the animals in small cages can be stressful.

4.42 Appropriate social contact and interaction has been demonstrated to be vital for the well-being of most commonly used laboratory species. Animals such as primates or dogs have evolved to form social groups with defined compositions and hierarchies. In their natural environment these animals usually have sufficient space to perform their social behaviours and maintain appropriate social distances. However, in the laboratory they find themselves in artificially composed groups and the cage or pen size that is provided in research facilities

34 See Smith AL and Corrow DJ (2005) Modifications to husbandry and housing conditions of laboratory rodents for improved well-being *J Inst Lab Anim Res* **46**: 140–7.

differs significantly from the space available in their natural habitats. The single housing of such animals requires special consideration.

### *Husbandry and care*

4.43 Many different aspects of routine husbandry and care can adversely affect the welfare of laboratory animals. Three important examples concern the effects of cage cleaning, lighting and sound.

- Cage cleaning

In contrast to humans, laboratory rodents are highly dependent on olfactory cues and communication, since they recognise their cage mates, social hierarchies and territories largely by smell (see paragraph 4.16). Routine changing of their bedding and sterilisation of cages, which removes their olfactory landmarks, can cause significant disorientation. The frequency of cage cleaning therefore requires careful consideration to strike a balance between the needs for hygiene, minimal disturbance and maintenance of habituation to humans, but the optimum frequency is not currently known.[35]

- Light

Other sources of harm can result from lack of attention to species-specific features such as biorhythms. Rodents are nocturnal and are most active in twilight, yet they are often housed in bright light and used in procedures during what would be their sleep phase.

- Sound

Rodents are sensitive to ultrasound. Although ultrasound is a normal part of the environment for rodents, exposure to sources of ultrasound produced by some electrical equipment, such as oscilloscopes and monitors, may be a source of stress.

### *Handling and restraint*

4.44 The way that animals are approached and handled has the potential to cause fear and distress, particularly in prey species or if the animal has had a previous adverse experience. Capture and holding is commonly stressful for rats, even when they have been habituated to handling.[36] In many cases, they have been shown to be able to anticipate what is about to happen to them if there are appropriate cues. It is plausible to assume that they can foresee the consequences of the administration of a substance if this has happened to them before.

4.45 Methods of restraint can also cause distress. For example, during toxicological testing, rats may be placed in polycarbonate tubes so that their snouts protrude from a hole at one end. A test substance might be delivered over the nose of the animals for periods of up to an hour, sometimes up to five times a day for several weeks or months. A recent report has indicated that a session of tube restraint is usually a stressful procedure.[37]

4.46 Close contact with humans can both improve and impair the welfare of laboratory animals. Social animals such as dogs or primates can benefit from establishing a relationship with

35 Some research has been carried out in this area. See, for example, Reeb-Whitaker CK, Paigen B, Beamer WG *et al*. (2001) The impact of reduced frequency of cage changes on the health of mice housed in ventilated cages *Lab Anim* **35**: 58–73.

36 Meaney MJ, Mitchell JB, Aitken DH *et al*. (1991) The effects of neonatal handling on the development of the adrenocortical response to stress: implications for neuropathology and cognitive deficits in later life *Psychoneuroendocrinology* **16**: 85–103.

37 The method can also pose problems if the tubes are of the wrong size and shape for the animal. The animal could try to turn around, become stuck, distressed and, at worst, die if the researcher selects the wrong size and if the animals are left unobserved. See Jennings M, Batchelor GR and Brain PF (1998) Report of the Rodent Refinement Working Party: Refining rodent husbandry: the mouse *Lab Anim* **32**: 233–59.

staff at research facilities. Establishing appropriate relationships is of special relevance to many types of primate research, where the researchers depend on the cooperation of the animal to perform certain tasks (see Box 5.4). Problems may arise if there is a frequent change in personnel. Appropriate handling of animals is also required when animals are removed and re-introduced to and from their social groups, which can cause fear and distress. Reintroducing animals may result in increased aggressive behaviour, as hierarchies are re-established.

4.47 Restraint for primates is another cause for concern. This is particularly so when animals have not experienced adequate habituation and socialisation to humans, and when those interacting with the animals are not sufficiently familiar with the species-specific behaviour. A number of restraint methods are used for different purposes. For example, restraint chairs are used to support primates in a stable sitting position when the experiment requires that they sit still for a prolonged period of time.[38] If the chair is incorrectly designed it could have an adverse effect on the animal's physiology,[39] and its welfare,[40] as well as on the validity of the scientific study being undertaken. Training the animal with positive reinforcement so that it cooperates during the procedure is important to minimise negative welfare effects.

### *Identification*

4.48 Scientists often need to mark experimental animals permanently so that they can be identified throughout the duration of a project. This can sometimes be achieved using non-invasive techniques such as noting coat patterns or applying non-toxic stains. Other methods include inserting microchips under the skin, which can cause momentary pain, or more-invasive techniques which include marking the ears using tags, notches or tattoos. Primates may be tattooed on the chest or fitted with collars. Methods used for amphibians include tattooing on the abdomen, sewing coloured plastic beads onto the muscle mass of the leg or back, attaching tags to the webs of the feet and freeze-branding (see paragraph 5.4). In field studies, toes may be removed from mice and frogs as a means of identification. This is usually a painful procedure which also affects normal behaviour and in some cases the animals' survival chances.[41]

### *Procedures and their effects*

4.49 The technical procedures to which animals are subjected can cause a range of negative states such as discomfort, pain, distress, fear and anxiety, either during or as a result of procedures. Some examples of common types of procedure are given below. More specific information on the effects of various types of experiment or animal model is provided in the relevant sections of Chapters 5–9. Refinements, which can and should be put in place to lessen the effect of any procedure, are described in Chapter 12.

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38 The duration of such restraint varies. A recent paper reported a device suitable for restraining marmosets for up to three days continuously, which would be an unusually long period of time. See Schultz-Darken NJ, Pape RM, Tannenbaum PL, Saltzman W and Abbott DH (2004) Novel restraint system for neuroendocrine studies of socially living common marmoset monkeys *Lab Anim* **38**: 393–405. More commonly, primates experience between three- and five-hour-long sessions several times per week, over a period of months. See, for example Box 5.4.

39 Norman RL and Smith CJ (1992) Restraint inhibits luteinizing hormone and testosterone secretion in intact male rhesus macaques: effects of concurrent naloxone administration *Neuroendocrinology* **55**: 405–15.

40 Klein HJ and Murray KA (1995) Restraint, in *Nonhuman Primates in Biomedical Research: Biology and Management*, Bennett BT, Abee CR and Henrickson R (Editors) (New York: Academic Press), pp286–97.

41 See May RM (2004) Ethics and amphibians *Nature* **431**: 403.

***Administration of substances***

4.50 Many experiments begin with the act of administering a substance to an animal, the effects of which may not be limited merely to a pinprick or a change in diet. We describe below a range of generic effects that may arise for rats used for the purpose of safety assessments of a candidate pharmaceutical.

4.51 The administration process can be stressful and possibly painful unless the substance is being administered within a treat. The route chosen should be the most appropriate to produce the best-quality experimental results, and similarly, the most appropriate site needs to be used. This will most commonly be under the skin in the scruff of the neck, or intravenously. Occasionally substances may be injected into the joints, brain, muscle, skin, peritoneum, footpads, veins or arteries of an animal. Substances may also be introduced into the lung or nasal cavity (often under whole-body restraint), rectum or vagina. If very accurate oral dosing is required, the substance is placed directly into the stomach using a tube that is passed down the oesophagus or nose rather than being administered with a treat or food.

4.52 Once test substances have been administered, the animal is likely to experience some form of effect which depends on the nature of the substance administered and the end points of the procedure. For example, if the animal is a disease model and the compound is an effective therapeutic intervention, the animal will experience an improvement of the disease-specific symptoms. However, some compounds, and very occasionally the solutions that they are dissolved in, may also be irritants; for example substances that are highly acidic or alkaline. Other compounds may cause disease or may be given at toxic doses, in which case they could cause nausea, pain or seizures. The latter phenomena can result in significant suffering, even with the implementation of humane endpoints.[42]

***Removal of blood***

4.53 Much research involves the sampling of blood. Under ideal circumstances, this procedure only has relatively minor welfare implications for the animals, although it may sometimes cause discomfort, pain and distress, as is the case for human patients. Restraint is usually necessary, which can be stressful. In some cases animals such as primates are trained to co-operate in the process, for example by presenting a limb for sampling. This approach, which constitutes best practice, requires staff to be adequately skilled in the technique, as required by the provisions of the A(SP)A (see paragraphs 13.12–13.13).

4.54 Independent of the handling-related aspects of taking blood, further possible adverse effects can in some cases result from soreness, persistent bleeding (which may lead to the loss of a significant proportion of circulating blood volume in small animals) and the formation of blood clots. In very small animals, it can be difficult to access veins that are large enough for blood removal. Techniques such as refined capillary tube sampling have been developed to address this problem.[43] Sometimes more invasive and potentially painful techniques such as tail-tip amputation, or occasionally retro-orbital bleeding (taking blood from behind the eye) are used. The latter method is usually carried out under general anaesthetic, but if complications such as blood clots occur, the animal is likely to be in pain once it has regained consciousness.

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42 Ways of implementing Refinement and Reduction are discussed in Chapter 12. We note that in practice, if the effects of the compounds on the animals are unknown, pilot studies using a small number of animals are usually carried out to ascertain the optimum dose, so that any adverse effects can be kept to a minimum.

43 Hem A, Smith AJ and Solberg P (1998) Saphenous vein puncture for blood sampling of the mouse, rat, hamster, gerbil, guineapig, ferret and mink *Lab Anim* **32**: 364–8.

### *Surgery*

4.55 Animals used in research and testing may undergo surgery for a variety of reasons: to implant osmotic minipumps for delivery of substances or telemetry devices (see paragraph 4.56), to ligate nerves or blood vessels for 'models' of pain or stroke and to test medical devices such as pumps to assist the heart or to open the skull in order to form lesions of the brain for neurological studies. Surgery is carried out using appropriate anaesthesia and pain relieving medicines are also widely used. Although such provisions greatly reduce the impact of the actual intervention, animals may experience varying levels of discomfort or pain following surgery. They must therefore be monitored closely in the recovery period in order to minimise any negative effects.

### *Telemetry*

4.56 Telemetry is a technique that is being increasingly used and one that is often introduced as a refinement (because it enables large quantities of data to be obtained without restraining animals), or as a means of reduction (because more information can be obtained from one animal). Nevertheless, there are three possible sources of harm associated with telemetry that need to be considered in order to minimise implications for welfare. First, surgery is required to implant transmitters or loggers in most cases; secondly, devices have a physical impact on animals that can be significant, especially in rodents (they can weigh up to ten percent of the body mass[44]); and thirdly, most commercially available devices at present transmit at the same frequency, a problem that is frequently addressed by housing animals individually.

### *GM animals*

4.57 As we have said, there are concerns about the unpredictable consequences that the deletion or addition of one or a combination of genes may have on animals that have been modified (see paragraphs 3.41–3.43). It has frequently been pointed out that many modified animals are phenotypically 'normal' in appearance and that they do not experience compromised well-being. One report suggested that no more than ten percent will experience harmful consequences. Another analysis, based on reports on GM mice made to the Danish Animal Experiments Inspectorate, found that 21 percent of strains were reported as experiencing minor discomfort, 15 percent experienced severe discomfort and 30 percent suffered increases in mortality and susceptibility to disease.[45] Since possible harms can only be assessed on a case by case basis, we consider specific examples in Chapters 5 and 7.

4.58 There are a range of implications for welfare which may arise during the creation and use of GM animals. For example:

- In small species such as rodents, surgical procedures are required for the transfer of embryos into recipient females. These procedures can be painful, and pain relief may also be required following surgery.
- All animals that are used in GM procedures must be tissue-typed to ascertain whether or not they actually have the desired modification. There are four main techniques for tissue-typing mice: saliva sampling, removing tissue from the ear, removing the tail tip or removing blood from the tail. A commonly used protocol is tail-tipping, which is painful

44 Morton DB, Hawkins P, Bevan R *et al*. (2003) Seventh report of the BVAAWF/FRAME/RSPCA/UFAW Joint Working Group on Refinement: Refinements in telemetry procedures *Lab Anim* **37**: 261–99.

45 Reported in BVAAWF/FRAME/RSPCA/UFAW Joint Working Group on Refinement (2003) Sixth Report: Refinement and reduction in production of genetically modified mice *Lab Anim* **37**: 3, Supplement S1–49, available at: http://www.ingentaconnect.com/content/rsm/lab. Accessed on: 21 Apr 2005; Thon R, Lassen J, Kornerup Hansen A, Jegstrup IM, Ritskes-Hoitinga M (2002) Welfare evaluation of genetically modified mice – An inventory study of reports to the Danish Animal Experiments Inspectorate *Scand J Lab Anim Sci* **29**.

for even very young pups. It involves cutting through nerves and bone and can lead to the formation of neuromas, which may give rise to 'phantom limb' type pain. A less invasive but still painful alternative is ear notching, which does not require cutting through bone and can be combined with identification.

- Recipient female mice are mated with sterile or vasectomised male mice so that the transferred embryos have an increased chance of implantation and development. While it is desirable to use small and passive males, large, aggressive animals might also be used to mate small, immature females, which can cause stress and even injury.
- The different methods of producing GM animals vary in their efficiency. Some often entail increased fetal mortality (see Box 5.6).

***Euthanasia***

4.59 Euthanasia literally means a 'good death', and should not, if it is carried out properly, cause animals any pain, suffering or distress. Whether it is wrong to prematurely end an animal's life is a subject of debate (see paragraphs 3.47–3.49). Apart from the question of whether an animal is harmed by being killed, in the case of sociable animals such as dogs or primates, the implications for other members of the group of losing a group member also need careful consideration.

## Summary

4.60 In the first part of this Chapter we considered philosophical and evolutionary aspects of assessing pain, harm, distress and suffering in animals (see paragraphs 4.5 and 4.29–4.30). It is in principle impossible to get 'inside the mind' of an animal, however, just as with other humans, it is possible to make meaningful *approximations*. In the spirit of *critical anthropomorphism*, scientific evidence, based on objectively measurable clinical signs, can be combined with more subjective data, obtained, for example, by drawing on empathy. Humans must inevitably apply concepts such as pain, suffering and distress, which are used commonly and successfully in human–human interactions, when making welfare assessments for animals. These can be useful terms if applied with care. Care is also required when making inferences based on familiarity, empathy and methodological observation. Comparisons to human states have limitations in cases where animals are less similar to humans. Animals also may possess senses that humans lack, such as the ability to hear ultrasound. In assessing pain, harm, distress and suffering in animals it is therefore necessary not only to compare animals' capacities to those of humans, but also to examine their species-specific capacities and needs.

4.61 In the second part of the chapter we examined in more detail a range of possible sources of harm for laboratory animals. We considered several general issues that need to be taken into account relating to breeding, transport, housing, husbandry and care, handling, restraint, identification, procedures, adverse effects of the procedures, and euthanasia. For an adequate evaluation of the harms or 'costs' to research animals, the full lifetime experience of the animals must be carefully assessed and given due weighting. Whether or not the welfare of animals is negatively affected depends on the type of research, the standards of particular laboratory facilities that may vary in the way in which they seek to exceed minimum regulatory requirements, and the skill and motivation of those handling the animals to implement Refinements. It is practically impossible to make generalisations about likely costs to the animals, and each case of research needs to be considered individually. Further descriptions of welfare implications of specific types of research are provided in Chapters 5–9. We return to ethical issues raised by animal research in Chapters 14 and 15.

# Section 2

## Use of animals in scientific research

# Introduction to Section 2

In Section 2 we describe a range of different scientific uses for animals. We begin in Chapter 5 with basic or curiosity-driven research, which seeks to understand how animals develop and function. We refer to a number of examples, drawn from behavioural, physiological, developmental and genetic research. We then address the use of animals to study disease processes and consider two cases: rheumatoid arthritis and transmissible spongiform encephalopathies (TSEs) in Chapter 6. We also discuss the role of animal research in the discovery of the hepatitis C virus, the development of polio vaccine and diseases for which progress in producing treatments and cures has been more difficult (human immunodeficiency virus/acquired immune deficiency syndrome (HIV/AIDS) and cancers). We then turn to the use of GM animals for the study of disease, and explain the importance and relevance of comparative genetic research (Chapter 7). We go on to describe the use of animals in the development of medicines and vaccines by the pharmaceutical industry (Chapter 8) and then review the use of animals in toxicity testing of potentially hazardous compounds for humans, animals and the environment (Chapter 9). In each chapter, we consider welfare implications for the animals involved and aim to illustrate the predictability and transferability to humans of data gained from animal research by reference to specific examples. A summary of Chapters 5–9 is provided at the end of Section 2 in Chapter 10. The application of the Three Rs in animal research and testing is discussed in Chapters 11 and 12.

# Chapter 5

## The use of animals in basic biological research

# The use of animals in basic biological research

## Introduction

5.1 In this chapter, we are primarily concerned with the use of animals for basic, 'blue-sky' or curiosity-driven research (see Paragraphs 3.53–3.54). This kind of research aims to help us understand how animals develop and function at the behavioural, physiological, cellular and molecular levels. Knowledge produced in basic research has also contributed to medical advances. Several different types of animals are used, including invertebrates such as fruit flies and nematode worms, non-mammalian vertebrates (frogs, fish and chickens) and mammalian vertebrates such as mice, rats, rabbits, cats, dogs and primates. Almost all of the animals used are specially bred for this purpose, and approximately 80 percent of animal experiments carried out on vertebrates in the UK in 2003 involved mice or rats.[1]

5.2 A wide range of different experiments are performed in basic research, and we can only give selected examples here. For the sake of simplicity, we divide our discussion into the use of animals for the following purposes, which cover most types of research in this area:

- behavioural studies;
- physiological studies;
- studies on development;
- genetic studies; and
- the development of research tools and techniques, for example, antibody production, biopharmaceuticals and cloning.

### Comments on the use of animals in basic research from respondents to the Consultation

'…major developments in medicine and surgery have often been based on fundamental understanding of biological premises. These have required 'blue-skies' research, which, by definition, has no immediate or obvious application.'
*Biosciences Federation*

'…the genetic mechanisms of many species (nematode worms, fruit flies, fish or mice) work in precisely the same manner as in humans, and in the mouse there are counterparts for most human genes.'
*Sarah Johnson, member of the Ethical Review Panel at the MRC NIMR*

'The number of GM animals we use is rising fast. This process is best described as commodification. The moral problem is that animals are not computers or areas of land or other "resources".'
*Shaun Carey*

'The production of GM animals is not a perfect science and there are often many animals produced to develop the specific modifications that are required to meet research objectives. This results in a large number of mice required to be bred and many to be culled that do not have the specific genetic manipulation.'
*Canadians for Health Research*

## Behavioural studies

5.3 One of the great challenges to life scientists is to understand the biological basis of animal behaviour. Why do some birds sing when others do not? Why are some animals monogamous, and others promiscuous? What cues do birds use to navigate when they migrate over long distances?[2] How do animals learn and remember? There are many different types of behaviour to understand and many ways to study them. In the category of behavioural studies, we arbitrarily focus on observational research that does not usually involve injections, drawing blood, surgery, dietary manipulation or chemical treatment. They comprise studies in which animals are observed in their natural habitat or

1 Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (London: HMSO).

2 Invasive research on animals that has no expected or direct application to the human species raises different ethical issues than research which has possible application (see paragraphs 3.52–3.55). See Schrag B, Freeberg T and Anestidou L (2004) The Gladiator Sparrow: Ethical Issues in Behavioral Research on Captive Populations of Wild Animals: A Case Study with Commentaries Exploring Ethical Issues and Research on Wild Animal Populations *Science and Engineering Ethics* **10**: 717–34.

in an environment that has been changed for the experiment. In some cases, the welfare of the animals is unaffected. In other cases, some distress may be caused, for example, when animals are tagged in some way. This may involve catching and restraining them for the duration of the identification process. Tagging itself can be invasive and potentially harmful (such as the amputation of a toe, as sometimes done to amphibians, or the use of 'patagial tags', which are attached to the muscle of fish or blubber of cetaceans) or non-invasive (such as use of a leg ring for birds).[3] An animal's welfare may also be affected if it is released into a foreign environment where it may have to re-establish its territory (see paragraph 4.48).

***Observational research***

5.4 As an example of observational research, a songbird might be reared in the absence of other birds in order to determine whether the bird would normally learn to sing by hearing the song of other birds, or whether it has an innate ability. In other examples, rats or mice are observed as they run in mazes, swim to rafts or associate a sound or coloured light with the delivery of a 'reward', such as food, an aversive stimulus in the form of, for example, a bitter-tasting substance or a 'punishment', such as a minor electric shock, to investigate aspects of learning and memory. The exploratory behaviour of animals on exposure to a novel environment might be studied in order to distinguish the bold from the timid. When behavioural studies are undertaken in a laboratory, an animal's welfare may be affected if the experimental environment is incompatible with its species-specific needs; for example, if space or environmental enrichments are insufficient or lacking. To explore the cellular and molecular basis of behaviour in more detail, scientists whose work involves animals not only observe the influence of environmental manipulation, but also seek to directly manipulate the animal as we discuss in the following section (see Box 5.1).

## Physiological studies

5.5 We include here experiments involving surgical, dietary or drug treatment of animals that are directed at understanding biological processes at the physiological, cellular or molecular

### Box 5.1: Example of research – Manipulation of circadian rhythms and comparison of gene expression in the liver and heart of mice

Storch KF, Lipan O, Leykin I *et al*. (2002) Extensive and divergent circadian gene expression in liver and heart *Nature* **417**: 78–83.*

In many mammalian tissues, the expression of genes that are responsible for the daily timing of physiological processes is controlled by biological timing mechanisms called circadian clocks. In this study, researchers used mice to compare gene expression in the liver and heart. They found that many of the genes expressed were under circadian control, although there were substantial differences between the two organs with regard to the kinds of genes affected. The authors hypothesised from their results that circadian clocks have a specialised role in each tissue, and that the extent of circadian gene regulation meant that it influences many different processes. They concluded that their work addressed important aspects of circadian gene regulation that applied to all mammals and made comparisons between the genes in mice and those in plants and fruit flies.

The following methods were used: mice were synchronised to a 12-hour light/dark cycle for at least two weeks and then placed in constant dim light for at least 42 hours. The mice were subsequently killed at various intervals of a light/dark cycle and their tissues collected and analysed. The mice would have experienced mental and physical disruption in their daily rhythms for the period that they were kept in constant dim light.

* This is an example of animal research that has been carried out in the UK and published in a peer-reviewed journal. Details relate to this specific example and should not be taken to represent a 'typical' animal experiment. It is important to note that individually published experiments usually form one part of a continuing area of research, and the significance of the results may therefore be difficult to interpret.

3 These identification methods have recently been criticised on scientific and animal welfare grounds, since there is some evidence that they can lead to increased mortality after release. See May RM (2004) Ethics and amphibians *Nature* **431**: 403.

levels. Better understanding of these processes has historically contributed to the body of scientific knowledge on animal and human biology. It has played an important role in the discovery of treatments for diseases, usually as a result of systematic methodological enquiry, and in some cases serendipitously (see Box 5.2).

### Box 5.2: Examples of how basic research has lead to unexpected clinical benefit

***Narcolepsy***

Narcolepsy is a disabling sleep disorder estimated to affect between three and five people per 10,000 in European populations.* Affected individuals have overwhelming feelings of sleepiness and fatigue. They may also experience dream-like hallucinations and the sudden onset of paralysis lasting for a few seconds, usually brought on by strong emotion. The cause and nature of narcolepsy were unknown until recently. In 1998 two groups, neither of which was working on narcolepsy, independently identified a neurotransmitter made by the hypothalamus in the brain; one group called it hypocretin and the other called it orexin. When the gene encoding the neurotransmitter was experimentally inactivated in mice, the mice developed narcolepsy.† The following year, a group studying an inherited form of narcolepsy in dogs isolated a defective gene, and found that it encoded a membrane receptor for one of the two forms of orexin/hypocretin.‡ Based on the evidence that defects in the orexin/hypocretin signalling system caused narcolepsy in mice and dogs, two research groups examined the brains of deceased humans who had suffered from narcolepsy. They found that orexin/hypocretin-producing cells in the hypothalamus were greatly decreased or absent.∫ It is now thought that narcolepsy in humans is usually caused by the autoimmune destruction of these cells in the brain, much as type I diabetes is usually caused by the autoimmune destruction of the cells that produce insulin in the pancreas. Identification of the biological basis of narcolepsy is thus a significant step in developing more effective ways of treating the disorder.

***Myasthenia gravis***

Myasthenia gravis is a life-threatening disease in which muscles become progressively weaker with exercise. The annual incidence of new people diagnosed with the disease is between 0.25 and two per 100,000.** A crucial discovery relevant to the pathology of this disease was made in 1973 by researchers who were studying the structure and function of receptors of the chemical transmitter acetylcholine. They isolated and purified the receptors from the electric organ of electric fish (eels, skates and rays) and injected them into rabbits to raise antibodies against them for use in their research (see paragraphs 5.24–5.25). Unexpectedly, the rabbits developed what was identified to be myasthenia gravis.†† It was found that patients with myasthenia gravis make antibodies against their own acetylcholine receptors and that these 'auto-antibodies' are usually causally linked to weakening of their muscles. The receptors are normally on the surface of muscle cells and are activated when motor nerves release acetylcholine to stimulate the muscle to contract. In patients with myasthenia gravis, the anti-receptor antibodies inactivate the receptors so that acetylcholine is relatively ineffective. The presence of anti-acetylcholine receptor auto-antibodies is now widely used in the diagnosis of myasthenia gravis, and treatment is directed at removing or inhibiting the production of the antibodies. As a result of these pioneering studies, a number of other muscle and neurological diseases, such as Lambert–Eaton myasthenic syndrome and acquired neuromyotonia, were also found to be caused by the inactivation of receptors and channels by auto-antibodies.

* Zeman A, Britton T, Douglas N *et al*. (2004) Narcolepsy and excessive daytime sleepiness *BMJ* **329**: 724–8.

† Sakurai T, Amemiya A, Ishii M *et al.* (1998) Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behaviour *Cell* **92**: 573–85; De Lecea L, Kilduff TS, Peyron C *et al*. (1998) The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity *Proc Natl Acad Sci USA* **95**: 322–7.

‡ Lin L, Faraco J, Li R *et al*. (1999) The sleep disorder canine narcolepsy is caused by a mutation in the hypocretin (orexin) receptor 2 gene *Cell* **98**: 365–76.

∫ Peyron C, Faraco J, Rogers W *et al*. (2000) A mutation in a case of early onset narcolepsy and a generalized absence of hypocretin peptides in human narcoleptic brains *Nat Med* **6**: 991–7; Thannickal TC, Moore RY, Nienhuis R *et al*. (2000) Reduced number of hypocretin neurons in human narcolepsy *Neuron* **27**: 469–74.

** Vincent A, Palace J and Hilton-Jones D (2001) Myasthenia gravis *Lancet* **357**: 2122–8.

†† Patrick J and Lindstrom J (1973) Autoimmune response to acetylcholine receptor *Science* **180**: 871–2; See also pages of the Myasthenia Gravis Association website, including http://www.mgauk.org/mganews/0203-01.htm. Accessed on: 23 Apr 2005.

### *Study of the endocrine system*

5.6 Most of what we know about the endocrine system (which produces and releases hormones), has resulted from studies involving animals. Typically, hormone-producing endocrine glands, such as the thyroid, were surgically removed or chemically inactivated in adult animals. The effects of this treatment on the behaviour and physiology of the animals were analysed, and attempts were made to reverse them by administering extracts of the gland. If successful, the next step was to purify the active hormone(s) from the extracts. Most of the known hormones in humans were discovered in this way. Even today, newly discovered molecules that are thought to be responsible for signalling between cells are often tested by injecting them into

a living animal (usually a rodent). This is because those who undertake such research believe that this procedure is the most scientifically valid, and often the only way of determining hormone function in physiology and development. The welfare implications for the animals involved will vary depending on the kind of hormone and the dose administered. In humans, hormonal imbalances can cause unpleasant symptoms, including lethargy and headaches.

### Box 5.3: Example of research – How do monkeys view faces?

Guo K, Robertson RG, Mahmoodi S *et al*. (2003) How do monkeys view faces? – a study of eye movements *Exp Brain Res* **150**: 363–74.*

Perception of faces plays a crucial role in social communication. The aim of this research was to study accurately how faces are viewed by primates. The researchers investigated the organisation of eye movements in two adult male rhesus macaque monkeys in response to facial images. Previous studies had suggested similarities between humans and monkeys in the neural mechanisms responsible for the perception of faces. Thus, it was concluded that the results of this study could be compared to findings obtained from humans by less invasive means.

The monkeys underwent an operation under anaesthesia to implant a head-restraint device (see paragraph 4.47). Coils were then surgically implanted into the white, outer layer of the eyeball (the sclera) so that eye movements could be recorded. During experiments, the monkeys were seated in 'primate chairs' (see also Box 5.5), which enable the head of the monkey to be fixed. The monkeys' eye positions were recorded while images of monkey and human faces were presented on a computer screen.

It was already known that when monkeys are shown faces of other monkeys, their eyes fix on the eyes in the image. This particular experiment investigated the visual process that occurs when the faces were unfamiliar to the monkeys, and when the images were inverted or scrambled. Differences in perceptual processing when either a monkey or a human face was shown were also assessed. It was found that the monkeys exhibited similar eye scan patterns while viewing both familiar and unfamiliar monkey faces, or while viewing monkey and human faces. There was a greater incidence of fixation of the eye region of all the face images, and particularly re-fixation of the eyes of unfamiliar faces during the first few seconds, confirming that the eyes are important for initial identification. However, it was found that the eyes in the scrambled face images were much less of a focus than those in the upright or inverted faces. The researchers concluded that, while viewing faces, the eye movements in non-human primates are controlled by more than one level of perceptual processing; i.e. that the targeting of the eye region may occur at a relatively low level of visual processing (before identification of the object) and that the probability that the eyes will become the eventual target in the image is affected by higher levels.

With regard to welfare implications, the implants could have caused discomfort; the monkeys would also have needed to be carefully trained to avoid psychological distress caused by the restraint during the experiment. No reinforcements in the form of 'rewards' or 'punishments' were given during this procedure.

* This is an example of animal research that has been carried out in the UK and published in a peer-reviewed journal. Details relate to this specific example and should not be taken to represent a 'typical' animal experiment. It is important to note that individually published experiments usually form one part of a continuing area of research, and the significance of the results may therefore be difficult to interpret.

***Study of the immune system***

5.7 Many studies on living animals, involving mainly mice and rats, have been conducted to examine the vertebrate immune system, and most current knowledge is based on this research. The immune systems of animals and humans protect them from infection. If the adaptive immune system is challenged by a particular infectious agent that it has previously overcome, it is able to do so on subsequent occasions much more quickly and effectively. Research on the adaptive immune system usually involves an initial immunisation of animals with foreign (from another animal) biological molecules or cells or microorganisms such as bacteria. Immune responses are characterised by the production of immune cells and antibodies, which specifically recognise and help eliminate the foreign molecules, cells or microorganisms (all referred to as antigens). Experiments of this kind provided the first evidence that the cells responsible for adaptive immune responses were a class of white blood cells called lymphocytes. In these experiments, rats or mice were irradiated with X-rays to kill most of their white blood cells, including lymphocytes, rendering them unable to make adaptive immune responses. When different cell types were transferred into these animals, only lymphocytes were found to reverse this deficiency. The welfare of the animals

was usually affected because of increased susceptibility to infections, particularly in the gut, due to the destruction of the lining of mucosal cells caused by the irradiation. These infections were usually treated with antibiotics. In the first series of experiments of this kind, significant numbers of animals died, most likely due to diarrhoea. In general, it can be assumed that the experiments entailed at least some malaise for the animals involved.

5.8 These irradiation experiments depended on the availability of inbred strains of rats and mice, which are produced by repeated rounds of inbreeding until the animals within each strain are nearly genetically homogeneous. The use of these strains allows cells to be transferred between animals of the same strain without the problems of immunological rejection. If cell transfers are attempted between animals of different strains or species, the transferred cells are recognised as foreign by the immune system and the body mounts a reaction and tries to destroy them. Experiments in which skin grafts were transplanted between mice of different strains established that graft rejection is an immunological response. Studies of these immune responses, and the development of medicines that are able to overcome them, eventually facilitated organ transplantation in humans. Transplantation experiments cause some distress to the animals involved, partly because of the anaesthesia used and partly because bandaging the grafts may cause irritation.

5.9 The approach of transferring lymphocytes into the same inbred strain of irradiated mice or rats has also been used to show that different classes of lymphocyte mediate different types of immune responses. New subclasses of lymphocyte and response are still being discovered in this way. Since immune responses in mice and rats are remarkably similar to those in humans, many researchers have applied the knowledge gained from research in rodents to humans. It is also possible to transfer human lymphocytes to immunodeficient mice to enable the study of 'human' immune responses using mice. Such 'humanised' mice have been important in understanding the function of a range of viruses, including how HIV/AIDS destroys the human immune system and eventually causes the death of the patient. Since mice without a functioning immune system are highly susceptible to infections, they are usually kept in sterile environments, and enrichments are not commonly provided.

### *Study of cell differentiation*

5.10 Similar experiments involving cell transfer in mice are currently being carried out to study the potential of unspecialised stem cells to develop into various specialised cell types. Stem cells isolated from adult organs are called adult stem cells, whereas those isolated from early embryos are called embryonic stem (ES) cells. Experiments involving the transfer of mouse stem cells into irradiated, or otherwise injured, mice have contributed to knowledge about the potential of using human stem cells to treat conditions in which cells die, such as strokes, heart attacks, diabetes and Parkinson's disease (see paragraph 5.26).[4] Blood-forming stem cells from bone marrow have long been used to treat patients whose own blood cells had been destroyed by disease, irradiation or anti-cancer medicines. Welfare problems for the animals used in the experiments referred to above could result from the underlying disease, as well as from the cell transplantation procedure itself, which involves an injection of cells through the lining of the abdominal cavity or into the bloodstream or an organ.

### *Study of the nervous system*

5.11 Much of our knowledge about the functioning of the central nervous system (CNS) has come from invasive animal experiments in which parts of the nervous system are electrically monitored, stimulated or destroyed. Many studies have been undertaken in primates, as the

4 Nuffield Council on Bioethics (2000) *Stem cell therapy: the ethical issues* (London: NCOB).

cerebral cortex, which is responsible for most higher brain functions such as thought and speech, is very poorly developed in animals other than primates. For example, individual nerve cells or groups of cells in the cortex of a conscious monkey that are involved in anticipating a movement before it occurs can be distinguished from those cells that send the signal for the movement itself. In a similar way, it is possible to distinguish areas of the cortex involved in recognising the colour of an object from those involved in recognising motion of that object. Although non-invasive imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) now allow the physiological activity of large groups of nerve cells in the human brain to be studied, the resolution of these methods is still too poor to study individual nerve cells, or even small groups of nerve cells. Currently, therefore, the only way in which individual or small groups of cells can be studied is by inserting needle electrodes into the brain (see Box 5.4). Nonetheless, imaging techniques are rapidly improving and are likely to provide increasingly powerful alternatives to invasive animal research of this type (see Box 11.1).

### Box 5.4: Example of research – Studying control and function of the hand using primates

This is an example of animal research witnessed by some members of the Working Party during a visit to a research establishment.

The objective of this research involving macaque monkeys was to increase understanding of how a stroke can impair use of the hand in humans. It sought to investigate how activity in groups of brain cells in a part of the brain called the motor cortex controlled specific hand and finger movements. Primates were used because only these animals have a sufficiently similar brain structure, function and cognitive ability to ensure that the results were relevant to humans. Research of this type has recently made significant contributions to the diagnosis and therapy of movement disorders and has been crucial to the development of deep brain stimulation (DBS), a new treatment for Parkinson's disease.*

The monkeys were procured from a breeding colony in the UK where normal practice was to rear them in groups of 16–18 animals and accustom them to contact with humans. In the laboratory, the animals were housed in pairs from the age of 18 months. The cages measured approximately 2.40x1.80x1.20m (width/height/depth) and contained objects for enrichment such as toys, mirrors, puzzle boxes and swings. Foraging material was provided in one part of the cage. The room was lit with natural daylight through windows on two walls. In winter, the light was regulated on a 12-hour scheme with fading transitions. Researchers reported that they maintained frequent social contact with the monkeys.

This project and the procedures were classified as 'moderate' by the Home Office. The first procedure was usually an MRI scan. Under anaesthesia, three-dimensional scans of the monkey's skull and brain were taken. These pictures aid the accurate targeting of areas of the brain from which recordings are made.

The animals then underwent a period of training and learned that they would be rewarded with treats such as fruit, nuts and biscuits when they performed certain tasks correctly. Over a period of time, which varied between six and 12 months, they were also trained to remain still while the research was being carried out, which required the use of some degree of restraint to which they became accustomed.

The primary surgical intervention was the implanting of devices necessary to record specific nerve-cell and muscle activity. Under general anaesthesia, a head-restraint device and recording chamber were fitted. The implants weighed 150g and consisted of a metal ring of approximately 10cm in diameter and 1mm in thickness, which was attached to the monkey's head by means of four bone screws of about 3mm diameter. The screws were inserted through holes made in the skull and were fixed on the inside. These screws were subsequently used to attach the head of the monkey to a specially designed primate chair during an experimental procedure. During surgery, electrodes were also implanted to record the activity of the various nerve cells and muscles that are involved in moving the hand and arm.

After surgery, monkeys received post-operative care including pain relieving medicines and antibiotics and were monitored according to a regime approved by the named veterinary surgeon (NVS). The average recovery time to normal behaviour was two to three days. The recording procedure itself, which involved introducing very fine microelectrodes into the brain, is not painful, because the brain itself has no pain receptors. With regard to the psychological effects on the animals, there was usually a period of two to three days during recovery from surgery when the monkeys touched the implant. They then became accustomed to it and stopped doing so.

In order to allow for the recording of neural and muscular activity, the monkey was placed in a primate chair. This is a steel device, measuring approximately 70x30x30cm. Once the monkey was seated in the chair, a metal disk was put over the ring attached to its skull, thereby immobilising the head by connecting it to the chair. This is required to allow for the stable recording of the activity of single neurones. The monkey remained able to move its jaw and chew, and the rest of

*Continued*

the body was free to move. The monkey appeared not to resist this procedure (see paragraph 3.34). The multiple electrodes inserted through the implanted recording chamber into the monkey's brain were connected with wires to a computer, and to devices recording the activity of muscles in the arm and hand.

With regard to the experimental procedure itself, the standard task required the monkey to perform a highly skilled hand movement, using its thumb and index finger to squeeze two levers into precise target zones. Each time it squeezed the levers successfully, it was given a food reward by an animal technician sitting next to the monkey. Once researchers had obtained sufficient data on the connection between certain neural areas of the motor cortex and hand movements, the electrodes were inserted into a new area of the brain. There were typically three to five sessions per week, with regular breaks of three to four weeks. Each session lasted approximately three hours, during which a monkey received around 600 food rewards. On average, each monkey provided 100–200 fully analysed neurones over 18 months. Animals were killed at the end of this period by administering deep general anaesthesia from which they did not recover. This allowed electrophysiological and neuroanatomical investigations of brain pathways involved in hand control which enabled the scientists to verify the anatomical position of the electrodes that had been inserted during the research. At this particular laboratory, approximately one monkey per year was used for this type of research.

* DBS involves the implantation of small stimulating electrodes of approximately 1x3mm in the brain circuits of patients suffering from Parkinson's disease. The electrodes are connected with wires to a unit implanted close to the collar bone. This unit generates electrical impulses in a method similar to pacemakers. To date, approximately 22,000 patients have been treated with DBS. The technique helps to reduce dramatically the manifestation of tremors, episodes of spasticity and other forms of abnormal movement typically experienced by sufferers of Parkinson's disease. See Rodriguez-Oroz MC, Zamarbide I, Guridi J, Palmero MR and Obeso JA (2004) Efficacy of deep brain stimulation of the subthalamic nucleus in Parkinson's disease four years after surgery: double blind and open label evaluation *J Neurol Neurosurg Psychiatry* **75**: 1382–5; Kumar R, Lozano AM, Kim YJ *et al*. (1998) Double-blind evaluation of subthalamic nucleus deep brain stimulation in advanced Parkinson's disease *Neurology* **51**: 850–5.

## Studies of animal development

5.12 Developmental biologists often carry out experiments on embryos to determine the cellular and molecular basis of animal development. Parts of an embryo (often chick embryos) are removed to learn about how different tissues develop (see Box 5.5). In some cases, a fragment of tissue is transferred to a new location in the embryo to observe its development. The outcome indicates whether or not the tissue was already irreversibly programmed for development into a particular tissue or organ at the time of transfer. A dye might also be injected into one or more cells, to enable observation of their stages of development. Zebrafish embryos are often used because they are transparent, which is a useful property with regard to monitoring the development of injected cells in the living embryo.

### Box 5.5: Example of research – Developmental studies involving amphibians

This is an example of animal research witnessed by some members of the Working Party during a visit to a research laboratory. The main focus of the research was to improve understanding of the processes that determine cell differentiation during the early stages of embryonic development. Researchers used two different species in order to provide comparable information. Amphibian embryos were preferred to mammalian models such as the mouse because amphibians produce a large number of eggs that develop externally to the mother, are of a size which allows experimental reagents to be injected easily, and develop fairly rapidly. The research was undertaken on embryos of the frogs Xenopus laevis and Xenopus tropicalis. In general, the results gained from developmental studies on these frogs are considered to be readily transferable to mammals, including humans, as most of the basic developmental mechanisms have been highly conserved in evolution.

The stimulation of egg-laying was the only procedure undertaken in this study that fell under the A(SP)A. Adult female frogs were injected with a hormone that caused them to lay large numbers of eggs within 3-12 hours. This involved a subcutaneous injection just over the dorsal lymph sac. The eggs were fertilised artificially to ensure synchronous development. In order to do so, a male frog was killed by methods referred to in Schedule 1 of the A(SP)A, and its testes was removed and used to fertilise the eggs. Female frogs generate more eggs over a four month rest period and are reused in the procedure described above for the production of new eggs.

The frogs were kept in a windowless room in three rows of five basins, each measuring approximately 60x40x30cm. There were between five and 25 frogs per tank, each frog having a minimum of one litre of water. The water was changed daily. No enrichments were provided in the tanks. The room light operated on a 12-hour cycle, with gradual transitions between light and darkness.

### *Study of gene function in embryos*

5.13 Developmental biologists often seek to determine the roles of single genes in animal development. A useful way of doing this is to create GM animals in which the expression of a specific gene is increased or decreased (see paragraphs 5.19–5.20). For example, in some experiments, molecules of ribonucleic acid (RNA, an intermediary involved in the transfer of genetic information between DNA and proteins) are injected into early frog or fish embryos. This will transiently increase or decrease the expression of a specific protein, thereby helping to determine how that protein (and thereby the gene that codes for it) normally functions in early development. The welfare implications of such experiments are difficult to predict and, depending on the gene, could range from no adverse affects to severe developmental abnormalities and disability (see paragraph 4.57). It is for this reason that in this, and similar types of genetic research, endpoints are defined in licence applications and research should be stopped humanely if they are exceeded (see paragraphs 5.22 and 12.21).[5]

5.14 Embryologists who study early development in mice sometimes mix cells from embryos of two different mouse strains to form a mouse that is made up of cells from the two strains. If a specific gene in one of the sets of cells is altered before mixing them, the influence of that gene on the development of the altered cells (and the cells that derive from them) can be determined in an embryo in which many of the cells are unaltered. The mixed embryos need to be implanted into the uterus of a surrogate mother in order to develop. The mothers may then be killed in order to obtain the embryo at different stages of development. The welfare implications for the animals relate to the anaesthesia and implantation procedure for the surrogate mother and to any developmental abnormalities in the chimeric offspring.[6]

### *Study of development after birth in mammals*

5.15 Since development continues after birth in mammals, many studies in this area involve research on animals after they are born. Neurophysiologists, for example, first demonstrated the importance of a critical period in visual development by patching one eye of newborn cats and monkeys.[7] If this is done for one week during the first six months after birth, the covered eye becomes permanently blind as a result of alterations in the way in which nerve cells are interconnected in the brain. Patching after this time does not produce the same effect. The same phenomenon was later found in children with one lazy eye. These children are now treated with alternating left and right eye patching to maintain vision in the affected eye until after the critical period, as first demonstrated in kittens.[8]

## Genetic studies

### *Selective breeding*

5.16 Selective breeding has been used for many decades to create more productive, or higher yielding farm animals, and for the breeding of animals with particular features and characteristics, including some companion animals and 'show' animals. It has also been used

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5 See Wolfensohn S and Lloyd M (2003) *Handbook of Laboratory Animal Management and Welfare*, 3rd Edition (Oxford: Blackwell Publishing Limited), Chapter 4.

6 See Morton DB and Hau J (2002) Welfare assessment and humane endpoints, in *Handbook of Laboratory Animal Science: Essential principles and practices*, Volume I, 2nd Edition, Hau J and Van Hoosier GL (Editors) (Seattle, WA: CRC Press), Chapter 18, pp457–86.

7 Early work includes, for example, Wiesel TN and Hubel DH (1965) Comparison of the effects of unilateral and bilateral eye closure on cortical unit responses in kittens *J Neurophysiol* **28**: 1029–40; Wiesel TN and Hubel DH (1965) Extent of recovery from the effects of visual deprivation in kittens *J Neurophysiol* **28**: 1060–72.

8 Many of those opposed to animal research are concerned about certain types of basic research, and argue that the alleged benefits cannot justify the suffering involved (see paragraphs 3.52–3.55).

in medical research to investigate basic biological processes. Many mouse mutants have arisen spontaneously in colonies maintained specifically for experimental purposes. Some of these have been used as models of human disease, including diabetes, obesity and neurodegenerative diseases.[9]

***'Forward genetics'***

5.17 Other techniques seek to deliberately change the genetic complement of animals, in order to observe the consequences of these alterations. Classical genetic experiments (also called 'forward genetics') are performed by inducing random mutations. The animals are treated with mutagens such as X-rays, chemicals that alter genetic information or viruses that insert DNA into the host genome. Offspring are screened for abnormal features in development, physiology or behaviour. The advantage of this approach is that when a mutated gene is found, it is likely to be important for the feature that is abnormal in the mutant. The mutant gene can then be identified, by comparing gene sequences from the mutated animal to those from normal animals. This procedure has become much more straightforward since the genomes of a number of animals have been mapped and sequenced.

5.18 Until recently, these studies were mainly carried out in fruit flies and nematode worms, organisms which are small, low cost and have rapid generation times. These are crucial features for large-scale genetic studies that involve many thousands of animals. Genetic screens in flies and worms have contributed to many important advances in our understanding of animal development. Many of the genes identified were later shown to be common to all animals, including humans, and they often function in very similar ways. The conserved functions of particular genes have been demonstrated by transferring them, for example, from humans to worms or flies, and showing that they function in the same way. This research has revealed a remarkable degree of conservation of genetic information during evolution. More recently, large-scale genetic screens have been carried out using zebrafish and mice, primarily to discover the genes responsible for a particular developmental or physiological process. The welfare implications of such experiments are difficult to predict and, depending on the genes involved, could range from no adverse affects to severe developmental abnormalities and disability (see paragraph 5.13).

***'Reverse genetics'***

5.19 Another genetic approach, called 'reverse genetics', is mainly applied to mice. Researchers can alter a specific gene of unknown function either by over-expression (in *transgenic* mice), elimination (in *knock-out* mice) or replacement with an altered form of the gene (in *knock-in* mice). The genetic change is then passed on from generation to generation in the new, genetically engineered mouse strain, in which the function of the gene under study can be analysed.

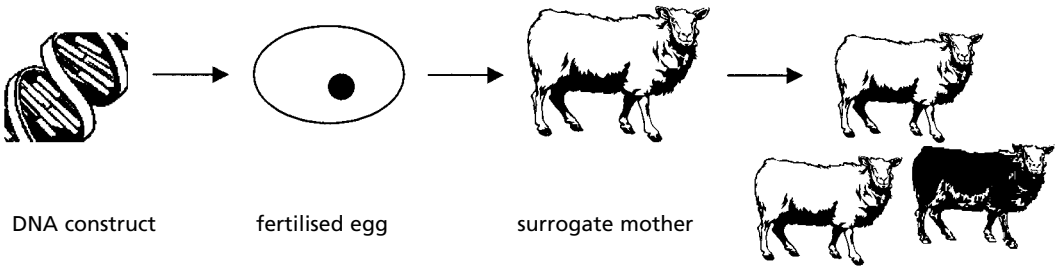
5.20 In order to over-express a gene, DNA is injected into the nucleus of a fertilised egg, which is then implanted into the uterus of a surrogate mother. A gene might also be eliminated (knocked out) or altered (knocked in) in ES cells, which are then injected into an early mouse embryo so that the cells derived from the modified ES cells develop into the tissues of the developing mouse. If cellular descendents of the ES cells form germ cells (sperm or eggs), these chimeric mice will produce offspring that have the eliminated or altered gene. Further breeding will produce some mice in which the gene has been completely eliminated or in which only the altered form of the gene is present (see Box 5.6).

9 See Schuler AM and Wood PA (2002) Mouse models for disorders of mitochondrial fatty acid ß-oxidation *Inst Lab Anim Res* **43**: 57–65.

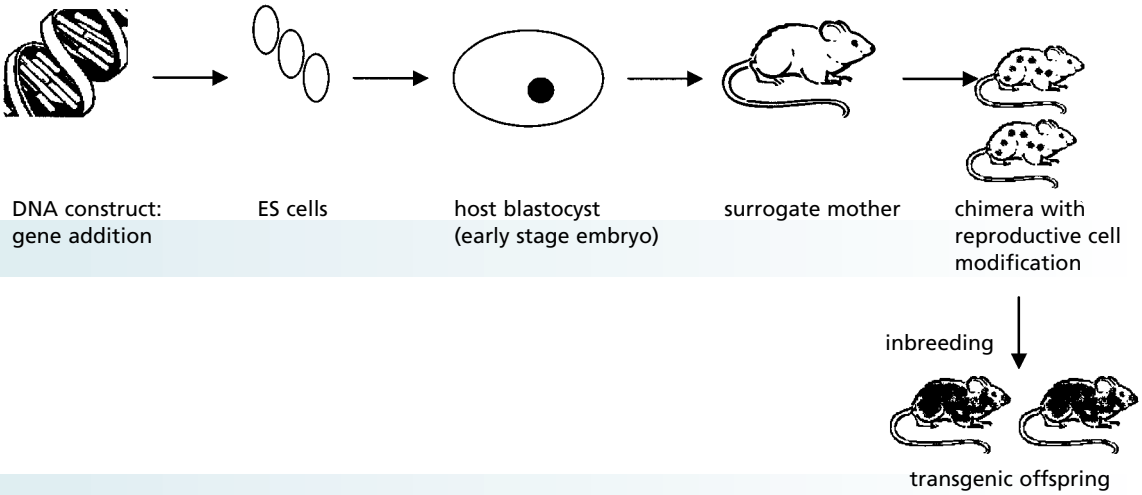
5.21 A specific gene can also be altered, over-expressed or deleted in particular cell types or at specific times, providing even more precise ways of studying gene function in animals. There

## Box 5.6: Common techniques for creating transgenic animals

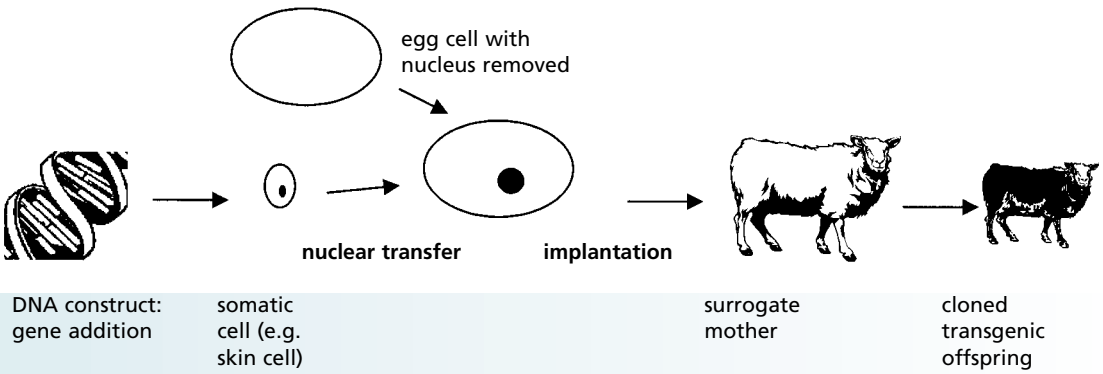
### Pro-nuclear injection




### Embryonic stem cells




### GM followed by nuclear transfer




***Pro-nuclear injection***

In the 1980s the first transgenic animals were created by pro-nuclear injection, which allowed only random introduction of new DNA sequences into the genome.* DNA is injected into a fertilised egg that is then transferred to a recipient female. Only a small proportion of the injected eggs will produce a first-generation ('founder') transgenic animal containing the gene of interest. Therefore the resulting offspring need to be selectively bred in order to obtain a line of animals all with the desired traits. This method has been used in

*Continued*

mice, rats, pigs, sheep, cattle and goats. The efficiency is low as approximately three to five percent of the animals born as a result carry the transgene.*

***Embryonic stem cells***

ES cells can be used to modify the animals' own genes in a targeted way, although as yet this has only been successfully carried out in mice. DNA is manipulated in the ES cells before they are transferred to developing embryos. The technique allows for specific gene targeting, enabling the precise deletion or modification of specific genes. Correctly modified ES cells are identified and injected into a host blastocyst (an embryo at an early stage of development). This will develop into a chimeric animal consisting of both the host's original cells and the modified ES cells. Chimeric mice whose reproductive cells (sperm and egg cells) have arisen from the modified ES cells are then used as founder animals in selective breeding.*

***Nuclear transfer***

Nuclear transfer techniques (or 'reproductive cloning', see Figure 5.1) have been adapted to allow more precise modifications of the genome, allowing researchers to target specific genes. GM is carried out in a cultured cell before nuclear transfer. The nucleus from the modified cell is transferred to an oocyte (immature egg cell) which has had its nucleus removed. The oocyte and modified nucleus are combined through a process called 'cell fusion' and the resulting cell transferred to a recipient female. Viability and survival rates of embryos generated by nuclear transfer are low and it is estimated that less than three percent of the nuclear transfer embryos result in live offspring† (see paragraphs 5.28-5.29).

A relatively new technique involving the use of viruses to transfer DNA into the genome has the potential for much higher efficiency. It has been reported that 80–100% of the mice born following this technique are transgenic.*

* See Clark J and Whitelaw B (2003) A future for transgenic livestock *Nat Rev Genet 4:* 825–33.

† Roslin Institute (2002) Somatic Cell Nuclear Transfer (Cloning) Efficiency, available at: http://www.roslin.ac.uk/public/webtablesGR.pdf. Accessed on: 25 Apr 2005.

are between 22,000 and 25,000 genes in the mouse genome, and several hundred have already been specifically eliminated in mice. In principle, all of the remaining genes could be deleted in further studies, alone or in combination with other genes. Not all of these procedures would result in viable offspring, as the elimination of some genes would lead to the death of the developing embryo. However, more sophisticated techniques have been developed, such as producing 'conditional knock-out' animals, in which the gene deletion is only triggered for experimental purposes or in specific tissues.[10]

5.22 The welfare implications for animals used in these kinds of experiments cannot be predicted because it is not known beforehand what type of defect may be produced by the genetic modification (see paragraph 4.57). As we have said, licences require that research is stopped and animals are killed humanely if defined thresholds of pain or suffering are exceeded (paragraphs 5.13 and 12.21). Although many of the mice created have no obvious abnormality, others have severe developmental defects. For example, mice in which a growth factor receptor gene was knocked out had severe abnormalities including skeletal defects and profound deafness.[11] The methods by which GM animals are produced also have the potential to be painful and distressing (paragraph 4.58). Large numbers of animals are used to produce a single GM strain due to the relatively low efficiency of the methods used to achieve genetic modification. Usually, the majority of the animals that are produced do not have the desired genetic traits and are usually euthanised (see Box 5.6). More efficient methods would be desirable. Many strains of GM animals are expected to be established in the future. For example, it has been predicted that 300,000 new genetic lines of mice could be created over the next two decades.[12]

### *Study of protein and cellular function*

5.23 Genetic modification can also be used to produce mice that express a fluorescent form of a particular protein under study. This intervention allows researchers to observe the location

10 For a review, see Cohen-Tannoudji M and Babinet C (1998) Beyond 'knock-out' mice: new perspectives for the programmed modification of the mammalian genome *Mol Hum Reprod* **4**: 929–38.

11 Colvin JS, Bohne BA, Harding GW, McEwen DG and Ornitz DM (1996) Skeletal overgrowth and deafness in mice lacking fibroblast growth factor receptor 3 *Nat Genet* **12**: 390–7.

12 Abbot A (2004) Geneticists prepare for deluge of mutant mice *Nature* **432**: 541.

of specific proteins in living cells and to analyse their activity. The cells expressing these fluorescent proteins can be readily visualised in tissue using a fluorescence microscope and purified using a fluorescence-activated cell sorter. Fluorescent proteins themselves are not known to cause adverse welfare effects. Mice can also be engineered to express a toxic protein in a specific cell type so that cells of this type can be eliminated by the body. This technique is used as an effective way of determining the normal function of a particular type of cell.[13] Adverse effects on the animal would depend on the cell type that is eliminated.

## Research tools and techniques

### *Production of antibodies*

5.24 Antibodies are proteins that are widely used in many areas of biomedical research, as well as in clinical medicine. They are highly useful tools, as each antibody type recognises the specific 'foreign' molecule (antigen) against which it was produced. Antibodies of a particular type can therefore be used to identify, localise, quantify or purify an antigen. For example, antibodies might be labelled with fluorescent dyes and then used to locate specific molecules by fluorescence microscopy of tissues *in vitro* (i.e. in a tissue sample in the laboratory). They can also be labelled with enzymes and used to quantify specific molecules in blood or other fluids or tissues, as for example in the common pregnancy test. Antibodies are also used to purify cells or molecules by attaching them to magnetic beads. The antibodies bound to the cells or molecules of interest can then be 'attracted' out of solutions.

5.25 Antibodies are made by B lymphocytes, which develop in the bone marrow. In order to produce antibodies against an antigen of interest, an animal (usually a mouse, rabbit, sheep or goat) is administered with the antigen one or several times (immunised), together with a stimulant (an adjuvant), and the antibodies that are activated in response are then collected from the blood. Adverse effects depend on the dose, frequency of injections and the use of adjuvants, which can lead to irritation and the formation of an abscess. Immunisation can also occasionally lead to a severe allergic reaction (anaphylaxis), which can be fatal. If animals are used for the production of purified *monoclonal* antibodies (the ascites method), then serious adverse effects can occur. This procedure is rarely used in the UK, although antibodies made by this method may be imported from abroad.[14]

### *Animal cloning*

5.26 The term cloning refers to the process of creating an identical copy of a gene, cell or a whole animal. Two types of cloning need to be distinguished: *reproductive* and *therapeutic*. The former is used to produce an animal that is virtually genetically identical[15] to the predecessor from which it was cloned (see Figure 5.1 and Box 5.6).

5.27 The main purpose of developing *reproductive cloning* techniques is to facilitate the targeted genetic modification of animals.[16] Research also seeks to explore their potential for novel medical applications such as providing organs for xenotransplantation (see paragraph 1.18). In addition, cloned animals could be used to rapidly increase the number of animals of a genetically identical strain and therefore might replace repeated inbreeding (paragraph 5.8). Cloned animals are being used to study age-related changes in cells, including cancers,

13 The specific use of GM animals as disease models is discussed separately (see Chapter 7).

14 No procedures were performed during 2003 in the UK using the ascites model. See Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (London: HMSO).

15 A very small fraction of DNA (16,500 base pairs out of a total of 3,000 million base pairs in the human genome) is external to the nucleus, and therefore comes from the donor egg rather than the donor nucleus.

16 See Clark J and Whitelaw B (2003) A future for transgenic livestock *Nat Rev Genet* **4**: 825–33.

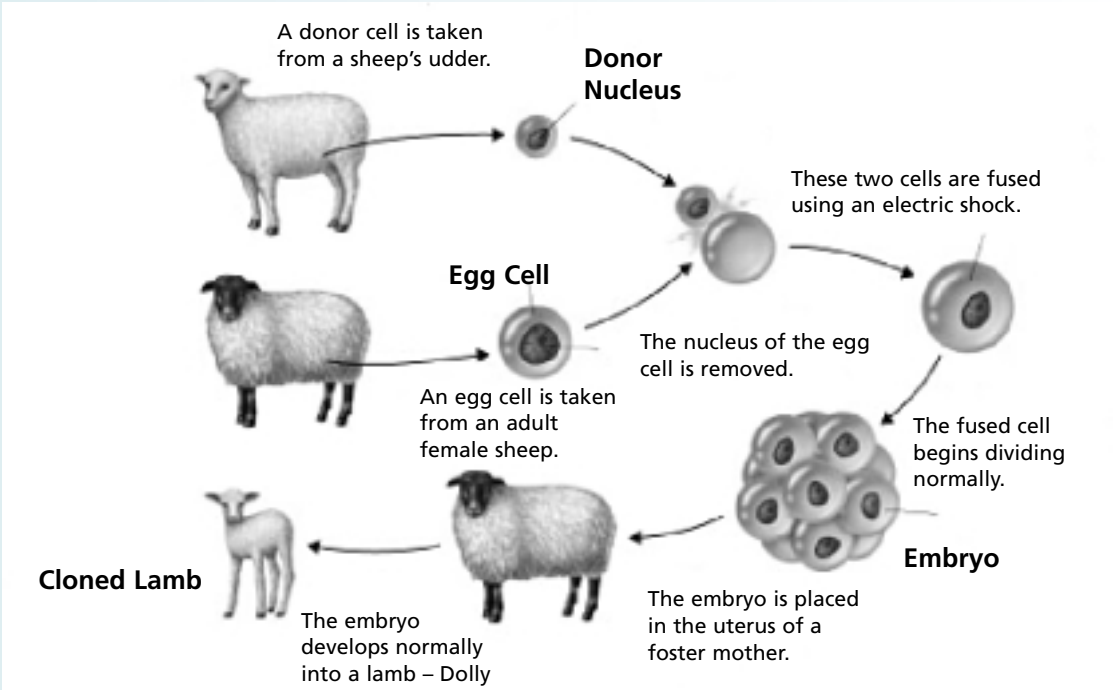



**Figure 5.1 Reproductive cloning of a sheep using nuclear transfer***

Dolly the sheep was produced using nuclear transfer. If the embryo is used to make ES cells for research rather than a new individual, the procedure is called 'therapeutic' cloning (see paragraph 5.30).

* Miller KR and Levine J (2003) Biology (New Jersey: Pearson Prentice Hall).

and some people are hopeful that the approach could help to conserve endangered species. A range of other purposes are possible in principle, such as the breeding of champion racehorses, the replacement of deceased pets or 'pharming' (see paragraph 5.31).

5.28 The first animals to be cloned from the nuclei of adult somatic cells were amphibians. This significant work using tadpoles in the 1970s showed that somatic cells (and not only reproductive cells) contained all the information required to develop into the organism.[17] In 1996, Dolly the sheep was the first mammal to be cloned from a cell from an adult animal, and the event attracted worldwide media attention (see Figure 5.1). Other animals that have now been cloned include the mouse, rat, cow, goat, pig, cat, rabbit, mule and horse.[18] Certain cloned animals have also been 're-cloned' to produce a second generation of clones.[19] Scientists are using these animals to study the longer-term effects of cloning, in order to assess any possible developmental abnormalities and welfare implications.

5.29 Reproductive cloning of animals raises a number of concerns. The method is currently highly inefficient, requiring repeated attempts to remove eggs and implant embryos to obtain even a single viable clone. The cloning of Dolly the sheep, for example, required the production of 277 fused embryos. Of this number, 29 cloned embryos were transferred into surrogate ewes, from which one pregnancy resulted.[20] More recently, 358 eggs fused with skin cells from a cloned animal yielded two re-cloned bulls, one of which died shortly after

17 Gurdon JB, Laskey RA and Reeves OR (1975) The developmental capacity of nuclei transplanted from keratinized skin cells of adult frogs *J Embryol Exp Morphol* **34**: 93–112.

18 See UN Educational, Scientific and Cultural Organization (2004) *Human Cloning* (France: UNESCO).

19 Kubota C, Tian XC and Yang X (2004) Serial bull cloning by somatic cell nuclear transfer *Nat Biotechnol* **22**: 693–4.

birth. Attempts to create a third generation of clones failed after 248 embryos were fused, six of which resulted in pregnancies, but all failed to develop into viable calves.[21] Cloning also has implications for animal health. Large offspring syndrome, in which the animals are too large for normal birth, occurs frequently, and cloned animals may also show signs of early aging. Dolly the sheep was euthanised in March 2003, six years after her birth, after suffering progressive lung disease and arthritis. These conditions are not uncommon in sheep of this age, and it is uncertain whether cloning was a factor.

5.30 The term *therapeutic cloning* is used to refer to the technique of producing ES cells that are genetically identical to the donor of the nucleus. ES cells, isolated from developing embryos, have the unique potential of being able to develop into different types of cells and to reproduce indefinitely. Therapeutic cloning could improve the prospects for the development of cell replacement therapy in humans. Genetically foreign cells (from another person) would be rejected unless the immune system was suppressed with powerful pharmaceuticals that may need to be taken for many years. However, if ES cells were produced from a cloned embryo made with the nucleus from one of the patient's own cells, they will be almost genetically identical. Cells and tissues made from these ES cells would not be rejected if transplanted into this patient (see paragraph 5.8). Advocates of this technique, currently being used in research with animals, hope that it could be used to treat patients suffering from conditions such as Alzheimer's disease and Parkinson's disease (see paragraph 5.10). Some preliminary work with cloned human embryos in the first few days of development has recently been licensed in the UK.[22]

***'Pharming'***

5.31 The term 'pharming' refers to the production of pharmaceuticals in plants or animals. Although, strictly speaking, pharming does not fall within the category of basic research, given its potential applications we consider it here as research in the area is still in its infancy. In plants, pharming generally involves the genetic modification of a crop plant in order to produce substances which can be extracted and processed into refined compounds. In animals, a potential pharming technique involves the transfer of human genes that encode specific therapeutic proteins. If the method is successful, the proteins which would be produced in milk, eggs or blood could be isolated for further processing. Sheep, goats and cows are used the most frequently in research on pharming as they produce relatively large quantities of milk. The production of these therapeutic proteins by other means can be technically difficult, expensive and time-consuming.

5.32 Clinical trials to test pharmed medicines have been initiated. The company PPL Therapeutics produced alpha-1 anti-trypsin (AAT), a treatment for emphysema and cystic fibrosis which was used in trials at hospitals in Europe, Canada, Australia and New Zealand. It was initially hoped that genetically engineered AAT would be on the market by 2007 but the project ceased in 2003. The European Medicines Agency (EMEA) is currently reviewing a Market Authorization Application for the pharmed pharmaceutical ATryn (human anti-thrombin).[23] It was developed to treat patients with hereditary anti-thrombin deficiency, a condition resulting in vulnerability to deep-vein thrombosis. The human gene for the required protein

20 Wilmut I, Schnieke AE, McWhir J, Kind AJ and Campbell KHS (1997) Viable offspring derived from fetal and adult mammalian cells *Nature* **385**: 810–3.

21 Kubota C, Tian XC and Yang X (2004) Serial bull cloning by somatic cell nuclear transfer *Nat Biotechnol* **22**: 693–4.

22 Human Fertilisation and Embryology Authority (HFEA) (2004) Press release *HFEA grants the first therapeutic cloning licence for research*, available at: http://www.hfea.gov.uk/PressOffice/Archive/1092233888. Accessed on: 24 Apr 2005; HFEA (2005) Press release: *HFEA grants embryonic stem cell research licence to study motor neuron disease*, available at: http://www.hfea.gov.uk/PressOffice/Archive/1107861560. Accessed on: 24 Apr 2005.

was inserted into an egg cell from a goat and activated only in udder cells so that it was possible to extract it from the goat's milk (see Box 5.6).[24] A number of other companies are also developing transgenic animal proteins.[25]

5.33 With regard to implications for animal welfare, there is some uncertainty as to whether the GM process may cause unexpected side effects. Genes may not always be expressed in the intended tissues or at appropriate levels, since insertion of microinjected DNA into the genome can be random (see Box 5.6). Advances in the process are aiming to overcome this problem, for example by designing the inserted DNA to ensure that it is only expressed in the intended tissue (a technique used in the production of ATryn). There are also concerns that the pharmed proteins might cause a toxic reaction.

## Summary

5.34 In this chapter we have discussed five areas of basic research: behavioural studies, physiological studies, studies on development, genetic studies and the use of animals in the development of research tools and techniques such as the production of antibodies and biopharmaceuticals. Research in all of these areas has provided much of what we know about biological systems and their functioning. While most of this activity has sought to contribute to the body of scientific knowledge, it has also led to the discovery of treatments for human diseases (see Boxes 5.2 and 5.4).

5.35 Basic research has enabled scientists to relate knowledge about animal behaviour to knowledge of animal physiology and, more recently, genetics. The results have been compared to human data to further knowledge of human biology and medicine. Genetic studies using animals have enabled the discovery of the location and function of individual genes, many of which play similar roles in a range of different species. We have discussed how research tools such as antibodies have proved invaluable for the development of molecular biology and how new techniques in genetics, including cloning and pharming, may allow advances in treatments for human diseases.

5.36 The impact of basic research on the welfare of the animals that are used is as varied as the types of research. It ranges from little impact to serious consequences for the animals' welfare. The former comprises research such as the observation of animals in their natural habitats, whereas the latter comprises research that changes the normal functioning of an animal through, for example, surgery or infection with a disease. New technologies, including genetic modification, cloning and pharming, also have the potential to adversely affect welfare. For example, the technical difficulties involved in cloning mean that a great number of animals are necessary to produce a single cloned animal. The number of animals that will be used in genetic research is expected to increase very substantially in the next few years. We noted, for example, that 300,000 new transgenic mouse lines could be created over the next two decades. A particular cause of concern regarding GM is that any implications for welfare are difficult to predict and that current techniques are relatively inefficient, requiring large numbers of animals for the production of a single GM strain.

23 GTC Biotherapeutics (2004) *ATryn® – Recombinant Human Anti-thrombin*, available at: http://www.transgenics.com/products/atryn.html. Accessed on: 24 Apr 2005.

24 See (2004) Down on the pharm *The Economist: Technology Quarterly Supplement* 16 Sept, pp34–5.

25 These include Nexia and Viragen. See Viragen *Avian Transgenic Technology*, available at: http://www.viragen.com/avian_intro.htm. Accessed on: 24 Apr 2005; Nexia Biotechnologies *Protexia™ – A Bioscavenger*, available at: http://www.nexiabiotech.com/en/01_tech/09.php. Accessed on: 24 Apr 2005.

# Chapter 6

## The use of animals in the study of human disease

# The use of animals in the study of human disease

## Introduction

6.1 In this chapter, we consider some of the principles and rationales of using animals as disease models. We examine in more detail two areas of recent medical advance: new therapeutic strategies for rheumatoid arthritis (RA), which also illustrates the contribution and use of non-animal models of disease, and the development of the scientific understanding of transmissible spongiform encephalopathies (TSEs), including bovine spongiform encephalopathy (BSE) and variant Creutzfeld–Jakob disease (vCJD). We also describe the role of animal research in the implementation of public health policies for protecting humans from exposure to TSE agents. These examples are followed by brief discussions of historically important animal disease models for hepatitis C and polio. We then consider two cases of diseases that have proved difficult to treat and cure, despite the availability of animal models: Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS) and cancers.

## The pathogenesis of disease

6.2 The study of the causes of disease is known as *etiology*. The mechanisms by which a disease develops, causes tissue damage and spreads within the body are known as *pathogenesis*. Understanding the etiology and pathogenesis of a disease is usually necessary in order to develop strategies to either prevent or limit disease. For example, a disease may be prevented by vaccination or the use of antibiotics. The effects of a disease may be limited by means of therapies and therapeutics that reduce inflammation or stop further tissue degeneration.

6.3 Most diseases are complex and involve dynamic interactions between molecular and cellular systems, which influence the development of the disease process.[1] Biologists who study a particular disease often use a variety of methods, both animal and non-animal, to investigate its mode of action. For example, pathogenesis studies with animal models are generally complemented by clinical, epidemiological and imaging studies using humans. While all of these areas are very important, researchers whose work involves living animals consider that their research plays a special role in the study of the pathogenesis of diseases of animals and humans, because it is often the most effective method of studying the complex interactions between molecules, cells and organs that occur in disease processes. For example, transferring a disease from one animal to another is commonly held to be the most reliable way to establish that a disease is caused by an infectious agent. This principle was first demonstrated in the 19th century when mice were injected with blood from cows infected with anthrax. The research showed clearly that the mice subsequently developed the disease.[2]

1 Examples include diseases in which high levels of antibodies and microbial or tissue antigens form immune complexes (a complex of antigen and antibodies in the blood circulation). These complexes can activate powerful inflammatory systems (the complement or coagulation cascades) that recruit different molecular and cellular systems into the process of pathogenesis. Effects include widespread damage to blood vessels (vasculitis), the kidney (nephritis), skin (dermatitis) or brain (meningitis).

2 The Nobel Foundation (1967) *Nobel Lectures, Physiology or Medicine 1901–1921* (Amsterdam: Elsevier Publishing Company), see *Robert Koch – Biography*, available at: http://nobelprize.org/medicine/laureates/1905/koch-bio.html. Accessed on: 12 Apr 2005.

### Comments on the use of animals for the study of human diseases from respondents to the Consultation

'To make any real progress in biological research there is no alternative but to use animals.'
*Professor Julian Blow*

'The fact that animal research provides essential information that is of benefit to both humans and animals is well proven and current available vaccines, surgical procedures and treatments available…support this argument. In many instances this information could not have been provided by any other method…'
*Institute for Animal Health, Compton Laboratory*

'Animals are important as biological processes are complex and cannot be replaced or simulated properly by computers.'
*Mr Kedarraja Kistnareddy*

'Research using whole animals has been fundamental to our understanding of whole-animal and whole-organ physiology for decades and will remain so indefinitely.'
*Dr RM Ridley and Dr HF Baker*

'It is not proved that animal research is a superior route to information. Transference of results can, and has, proved misleading.'
*International Primate Protection League UK*

'Whether rodents are the best animal to study for research related to human disease is debatable but practicalities dictate that these are often used and related results in the scientific literature are likely to focus on rodents.'
*Professor Bernie Hannigan*

'The only reliable model for a human is a human.'
*Anonymous*

## New therapeutic strategies for rheumatoid arthritis

6.4 RA is one of the most common human autoimmune diseases, affecting up to 600,000 individuals in the UK. It is a crippling disease resulting primarily in a chronic inflammation of joints of the hands, feet, knees, vertebrae or hips. It typically leads to progressive degeneration of the joint tissues with consequent disability and premature death. Although the exact cause of RA is unknown, in the last ten years there have been very considerable advances in the understanding of the molecular and cellular basis of the disease process. Animal models of arthritis have been used to study these processes and to devise and test new treatments. A successful treatment for RA has been developed, which has also led to therapeutic interventions for other chronic inflammatory conditions (see paragraph 6.10).[3]

6.5 There has been some debate about the relative relevance and contributions of *in vitro* and *in vivo* animal work to the study of RA. A review of the literature reveals that both animal models of arthritis and *in vitro* studies with human RA joint tissue have been used simultaneously and often by the same researchers. It would therefore be wrong to describe particular significant steps in the understanding of RA as having relied only on *in vitro* or *in vivo* methods. Experiments using both approaches relied on the results of previous experiments with animal and human tissue, live animals and human volunteers.

6.6 RA in humans is characterised by a chronic inflammation of the lining of the joint capsule (synovium). Inflammatory cells invade the synovial membrane of the joint, and there is excessive local secretion of molecules (cytokines) that produce inflammation. In the late 1980s, several groups of researchers started to examine the possible role of these molecules in RA after various cytokines were detected in the synovial fluid of patients.[4] It became clear by the early 1990s from studies on human tissue[5] and, later, in animal models of arthritis that the inflammatory process depends on a cytokine known as tumour necrosis factor alpha

3 Vilcek and Feldmann M (2004) Historical review: cytokines as therapeutics and targets of therapeutics *Trends Pharmacol Sci* **25**: 201–9.

4 For example, see Hopkins SJ and Meager A (1988) Cytokines in synovial fluid: II The presence of tumour necrosis factor and interferon *Clin Exp Immunol* **73**: 88–92.

5 A seminal discovery was made by Brennan FM, Chantry D, Jackson A, Maini R and Feldmann M (1989) Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis *Lancet* **2**: 244–7, who concluded that TNF plays a pivotal role in arthritis using inflamed tissues from patients of the disease; described later in Higgs G (2004) Molecular genetics: the Emperor's clothes of drug discovery? *Drug Discov Today* **9**: 727–9.

(TNFα).[6] Enhanced TNF production in the affected joints results in release of other cytokines and of growth factors that cause abnormal growth of new blood vessels, increased blood flow and destruction of cartilage. Once the crucial role of TNF became clear, it was proposed that neutralising TNF or switching off its production in the joint might reverse joint inflammation. Researchers were able to test the usefulness of neutralising TNF with anti-TNF antibodies,[7] both in *in vitro* studies with human joint tissue and in an arthritis model in rodents. In both cases, the antibodies reduced inflammation in joint tissue by binding specifically to the TNF molecules.[8] Thus, researchers used *in vivo* studies of rodent arthritis models to complement *in vitro* studies of human RA joint tissue to understand the pathogenesis of immune arthritis.

### *The rodent model for arthritis*

6.7 The rodent arthritis model is produced by the injection of bovine or chicken collagen,[9] together with a chemical that increases the resulting immune reaction, into inbred strains of mice or rats. Swollen joints and arthritis appear within 20–40 days. Although collagen-induced arthritis in the mouse does not exactly mimic RA in humans, it has a number of similarities. For example, the model allowed the primary role of TNF in joint inflammation to be examined, as it is common to both forms of arthritis. The mouse model for arthritis played a significant role in the development of the current and successful therapeutic intervention of blocking TNF to alleviate RA in humans.

6.8 Once arthritis develops, a painful swelling of the paws occurs, accompanied by erosions of the joint cartilage. In humans, painful swelling is accompanied by pain in the extremities. Similar effects resulting from the inflammation occur in mice, which may affect the welfare of the animal considerably since rodents use their front feet extensively for grooming, holding food, eating and moving around. Severely affected animals are usually euthanised before the end of the experiments.

### *Human clinical trials*

6.9 It had been demonstrated *in vitro* that antibodies against TNF (anti-TNF) reduced the production of other cytokines involved in the inflammatory response.[10] Subsequent animal experiments established that anti-TNF could be used to reduce the symptoms of inflammatory joint disease without seriously impairing the function of other tissues and organs. Clinical trials to assess the effect of anti-TNF reagents in humans began in 1992. Infliximab, a monoclonal antibody against human TNF, was used in a series of trials in patients to test the safety, efficacy and pharmocokinetics of anti-TNF therapy. The therapeutic dose used for the human trials was based on the mouse studies.[11] The clinical results in RA patients treated with infliximab demonstrated substantial benefits: patients reported alleviation of symptoms such as swelling, pain, stiffness, tiredness and lethargy

6 The abnormal synthesis of TNF by cells invading the joint capsule amplifies the inflammatory cell cascade, triggering the release of other inflammatory cytokines which cause tissue damage when present in excess.

7 Anti-TNF antibodies bind specifically to TNF molecules. For a description of the function of antibodies, see paragraphs 5.24-5.25.

8 Williams RO, Feldmann M and Maini RN (1992) Anti-tumor necrosis factor ameliorates joint disease in murine collagen-induced arthritis *Proc Natl Acad Sci USA* **89**: 9784–8. For a review and references to simultaneous work, see Vilcek and Feldmann M (2004) Historical review: cytokines as therapeutics and targets of therapeutics *Trends Pharmacol Sci* **25**: 201–9.

9 Collagen is a tough, fibrous protein that forms a major component of skin, tendons, bones, cartilage and other connective tissues. It helps to hold cells and tissues together.

10 Brennan FM, Chantry D, Jackson A, Maini R and Feldmann M (1989) Inhibitory effect of TNF alpha antibodies on synovial cell interleukin-1 production in rheumatoid arthritis *Lancet* **2**: 244–7.

11 Vilcek and Feldmann M (2004) Historical review: cytokines as therapeutics and targets of therapeutics *Trends Pharmacol Sci* **25**: 201–9.

a short time after being treated with the medicine. The first study was carried out in RA patients in which all other available therapies had failed. Following the success of this initial trial, larger studies were performed at four European centres.[12] These were followed by successful repeated-dose studies, which showed a long-term therapeutic benefit of the treatment.

6.10 Several types of anti-TNF treatments have now been approved by regulatory authorities in the USA and Europe and represent a major advance in the treatment of RA.[13] So far, more than 200,000 patients have been successfully treated, with marked improvement in their physical activity and quality of life. Anti-TNF therapy has now been adapted successfully to treat other chronic inflammatory conditions including inflammatory bowel disease (Crohn's disease), the rheumatic disease ankylosing spondylitis, psoriasis and psoriatic arthritis.[14]

## The transmissible spongiform encephalopathies

6.11 The TSEs are a cluster of degenerative brain diseases. The prototype TSE is scrapie in sheep, but a range of TSE diseases affect different species, including humans. Kuru is a human TSE that was once endemic in New Guinea. It was transmitted by ritualistic cannibalism, which involved eating the brain tissue of other people. The most common TSE in humans is Creutzfeld–Jakob disease (CJD), which occurs sporadically in the human population, with an annual incidence of about one person per million.[15] Kuru was the first human TSE that was shown to be transmissible and this was achieved by injecting brain material from patients into chimpanzees. A similar approach showed that CJD could be caused by a transmissible agent, whereas most other neurodegenerative diseases, such as Alzheimer's disease or Parkinson's disease, are not transmissible.

6.12 In 1986, a new TSE disease, BSE, was recognised in cattle. It reached epidemic proportions in the UK in the following few years, leading to over 180,000 cases. The origins of BSE have never been established, but it is thought that the epidemic was caused by the now-prohibited practice of feeding ruminant-derived meat and bone meal (MBM) to ruminants as a protein supplement. Evidence of infection with the BSE agent also appeared in zoo animals that had been fed MBM or bovine carcasses, and in domestic cats, which had presumably consumed bovine products in cat food and developed a feline form of BSE.

6.13 In 1996, the first human cases of a new type of TSE, known as vCJD, were observed in young people in the UK. The causative agent of vCJD was shown to be indistinguishable from the BSE agent and infection was presumed to have been caused by eating BSE-contaminated food. By April 2005, 155 cases of definite or probable vCJD had been confirmed in the UK with an average age of onset of clinical symptoms of 29 years of age, and median duration

12 Vilcek and Feldmann M (2004) Historical review: cytokines as therapeutics and targets of therapeutics *Trends Pharmacol Sci* **25**: 201–9.

13 In a further series of experiments involving the mouse collagen arthritis model, it was shown that the severity of chronic arthritis could be reduced with a combination of anti-TNF antibodies and antibodies against T cells. There later followed a Phase III clinical trial combining anti-TNF treatment with a conventional immunosuppressive treatment to inactivate T cells in the joint lesions. As in the case of the studies in mice, this refinement of anti-TNF therapy proved successful in halting the progressive degenerative changes in the joint cartilage and bone in affected joints in patients who were resistant to conventional drug-based treatment.

14 Vilcek and Feldmann M (2004) Historical review: cytokines as therapeutics and targets of therapeutics *Trends Pharmacol Sci* **25**: 201–9.

15 Three forms of the disease had been recognised prior to 1986, sporadic, inherited and iatrogenic (acquired through medical intervention). See The BSE Enquiry (2000) *Report of the BSE Enquiry*, Volume 2, Chapter 2, available at: http://www.bseinquiry.gov.uk/report/volume2/chaptea2.htm#817773. Accessed on: 12 Apr 2005.

of illness of 14 months, leading to death.[16] As the incubation period of TSEs can last for many years, the extent of human infection with the vCJD agent is unknown. For Kuru, the average incubation period was approximately ten years, but in some cases it exceeded 40 years. Thus, human cases of vCJD may continue to appear well into the 21st century. The BSE epidemic in cattle and the sudden appearance of previously unrecognised TSEs in humans and other species led to an unprecedented focus on experimental animal models of these diseases.

***The prion hypothesis***

6.14 For many years, the nature of the agent that caused TSEs was unknown. Research showed that they were not caused by classical infectious agents, such as viruses or bacteria. Lack of evidence that any form of DNA or RNA was involved led to the development of the *prion hypothesis*. According to this theory, TSEs were caused by a replicating abnormal form of a protein (a prion), which imprinted its configuration on normal molecules. This would allow prions to be transmitted between animals or humans, causing the disease. This novel hypothesis has subsequently been supported by a large number of experiments, most of which involved inducing TSE in animals.[17]

Animal models for TSEs: understanding the disease process

6.15 The pathogenesis of TSE diseases is complex and involves transfer and replication of the infectious agent (a prion), which spreads to the CNS via the blood or nerves. Prions do not induce an immune response. The pathology involves the accumulation of abnormal prion proteins in the brain and lymphoid tissues, and the degeneration of nerve cells (spongiosis). The pathogenesis of these diseases cannot be studied *in vitro* as they involve various physiological systems such as the alimentary tract, lymphoid tissue, nerve routes, peripheral ganglia and various brain regions.

6.16 One of the major steps in the study of the pathogenesis of TSEs was the development of experimental mouse models for the sheep disease scrapie, which had long been recognised as being transmissible between sheep. Transmission of the scrapie agent to mice (by injection of an extract of infected brain tissue from affected sheep into the brain) led to the development of a series of mouse models for scrapie. They were used to identify significant stages in the development of this disease and in defining the different strains of the infectious agent. These studies established that the agent was an abnormal form (PrPsc) of a normal protein (PrP). GM mice in which the PrP gene had been knocked out (see paragraph 5.19) were found to be completely resistant to scrapie, as there is no PrP protein for the PrPsc protein to convert to prions. With regard to welfare implications, mice involved in research on the developmental stages of scrapie typically experienced progressive neurological dysfunction, behavioural and gait abnormalities as well as weight loss. Researchers aimed to limit suffering by euthanising animals at the stage when they were unable to eat or drink without assistance. In some cases, animals were euthanised when they reached certain stages that were known to precede the experimentally induced terminal disease.[18] Other welfare implications may arise from the

16 The National Creutzfeldt–Jakob Disease Surveillance Unit (2005) *CJD Statistics*, available at: http://www.cjd.ed.ac.uk/figures.htm. Accessed on: 12 Apr 2005; World Health Organization (2002) Fact sheet: *Variant Creutzfeldt–Jakob disease*, available at: http://www.who.int/mediacentre/factsheets/fs180/en/. Accessed on: 12 Apr 2005.

17 For a description of the identification of BSE as a TSE, see The BSE Enquiry (2000) *Report of the BSE Enquiry*, Volume 2, Chapter 2, available at: http://www.bseinquiry.gov.uk/report/volume2/chaptea2.htm#817773. Accessed on: 12 Apr 2005.

18 As defined in, for example, Dickinson AG, Meikle VM and Fraser HJ (1968) Identification of a gene which controls the incubation period of some strains of scrapie agent in mice *Comp Pathol* **78**: 293–9; Thackray AM, Klein MA, Aguzzi A and Bujdoso R (2002) Chronic subclinical prion disease induced by low-dose inoculum *J Virol* **76**: 2510–7.

fact that some mice used in this type of research are allowed to age. They may therefore show signs related to old age, such as abscesses, starey coats (not lying flat) or holding their tails abnormally.

6.17 Similar experimental studies have demonstrated the transmissibility of BSE between cattle, sheep and primates. Transmission of BSE to monkeys by injection of bovine prions into the brains of macaques was the first demonstration that BSE was able to cross the species barrier from ruminants to primates. These experiments, undertaken in 1996 in the UK and France, were a forewarning that BSE might be transmissible to humans.

6.18 As there is no immune response to prion infection, it has not yet been possible to develop diagnostic tests that demonstrate the presence of the disease before symptoms occur. Although there is now a range of biochemical markers for detecting the abnormal protein in potentially affected tissues, infection of mice remains the accepted standard for diagnosing prion diseases.

6.19 In view of the potential number of human cases, it is important to develop intervention strategies aimed at slowing down or preventing the spread of prions. This may eventually be achieved by treatment with medicines or through the development of a vaccine. A vaccine could theoretically stimulate the production of antibodies to PrPsc, thus preventing prion proteins from spreading *in vivo*. Scientists using animals in research with this aim assert that the development of effective therapeutic strategies is likely to depend on continued research on animals.

***The contribution of animal models for TSEs to public health policy***

6.20 The *in vivo* models for the pathogenesis of TSEs have had decisive influence on the development of policies for public health aimed at controlling these diseases in cattle and sheep, and to protect humans from further exposure to agents of animal TSEs.[19] The current public health measures are based on evidence obtained from experiments on the pathogenesis of TSEs in cattle, sheep, pigs and chickens. Without these studies, it would have been difficult to know how to devise and implement public health measures, other than to prohibit the eating of any animal products, since, at the time, researchers were not able to undertake the research by alternative, non-animal methods.

***BSE pathogenesis and public health measures***

6.21 In several large-scale studies on the pathogenesis of BSE, scientists infected calves by feeding them with an extract of cow brain taken from an animal with the disease. The spread of infectivity was then monitored in various tissues. Infectivity was determined by administering extracts of tissue to mice and assessing if they develop the disease (see paragraph 6.18). Several hundred cattle and several thousand mice were used in these experiments. These studies established unequivocally that BSE replicates early on in the gut lymphoid tissues and then spreads to other lymphoid tissue and via major nerves to the CNS. The highest levels of infectivity were found in gut-associated lymphoid tissue, major nerves in the head and neck, brain, spinal cord and collections of nerve cells embedded in the vertebral column known as the dorsal root ganglia. Little infectivity was detected in skeletal muscles.[20]

19 Experimental transmission studies in pigs and chickens, for example, showed that these animals are not susceptible to BSE when fed infected tissue, thus allaying fears that pigs and poultry, which were also exposed to infective MBM, could be infectious for humans through the food chain.

20 The BSE Enquiry (2000) *Report of the BSE Enquiry*, Volume 2, Chapter 3, available at: http://www.bseinquiry.gov.uk/report/volume2/chaptea8.htm#821257. Accessed on: 26 Apr 2005.

6.22 The results from these and many similar studies on the pathogenesis and transmission of TSE between animals have been used to develop policies for public health to prevent the transmission of BSE from cattle through the human food chain. Specifically, they led to the banning of bovine offal for human consumption, the removal of brain, spinal cord and dorsal root ganglia, and the deboning of beef intended for public consumption. Based on knowledge of the dynamics of the spread of prions *in vivo*, the pathogenesis studies also provided the evidence for the development of the initial *Over Thirty Month Scheme* (OTMS), whereby the UK Government was able to purchase, for slaughter and ultimate destruction, cattle which were over 30 months of age. This implemented EU Regulations that ordered the prevention of the sale of beef from cattle over this age for human consumption in the UK. The OTMS was a crucial element of legislation for public health, and it may well have averted a larger number of vCJD cases than experienced so far.[21]

***BSE pathogenesis studies in sheep – a model for vCJD***

6.23 Sheep are susceptible to infection with the BSE agent, and the dynamics of infection and spread of prions in peripheral tissues is similar to that of vCJD in humans. Thus sheep are commonly held to be a useful model for vCJD. Studies of scrapie in sheep were the first to show that prions could accumulate in the tonsils, and this was shown subsequently to be the case for vCJD. There followed an analysis of the prevalence of vCJD in the human population through retrospective studies on tonsils, and later appendices. The results provided the first information on the number of people that could be incubating the disease.

6.24 BSE pathogenesis studies in sheep also showed that blood can be infectious. BSE can be transmitted between sheep by blood transfusion and current experiments are aimed at identifying the blood fraction that contains infectivity. Scientists conducting these experiments are also interested in exploring the implications of human-to-human transmission of vCJD through blood and have guided UK policy for public health by limiting the potential for this type of spread of vCJD. In 2003, it was found likely that two people who died of vCJD were infected by blood transfusions. As a result, the Department of Health announced in 2004 that anyone who had received a blood transfusion in the UK since 1980 would no longer be able to donate blood themselves.[22]

## The discovery of the hepatitis C virus using the chimpanzee

6.25 We now consider a more historic example of animal research for the study of disease. The existence of a blood-borne hepatitis virus that was neither type A nor B was described in the 1970s, following the identification of both these types. Throughout the 1980s, assays were developed to try and identify the cause of what was then termed non-A, non-B (NANB) hepatitis. However, none of the tests were sufficiently reproducible or specific.[23] Therefore an experimental chimpanzee model was developed, as this species was the only non-human animal that could be infected with the NANB hepatitis agent, which is still not able to be propagated *in vitro*. The chimpanzee model was used to demonstrate that NANB hepatitis was indeed transmissible, and allowed the isolation and characterisation of the virus.[24]

21 In 2004–5, the UK Government is implementing a transition towards replacing the OTMS with testing for BSE in cattle of over thirty months of age. See Department for Environment, Food and Rural Affairs (2005) *BSE: Public health issues – Over Thirty Month cattle – FSA review of the OTM rule*, available at: http://www.defra.gov.uk/animalh/bse/publichealth/otm/review/index.html. Accessed on: 26 Apr 2005.

22 National Blood Service (2004) *Variant CJD and blood donation*, available at: http://www.blood.co.uk/pdfdocs/vcjd.pdf. Accessed on: 26 Apr 2005.

23 Farci P (2002) A commentary on the original *Science* paper (Choo QL, Kuo G, Weiner AJ *et al*. (1989) Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome *Science* **244**: 359–62) *J Hepatol* **36**: 582–5.

24 Farci P (2002) A commentary on the original *Science* paper (Choo QL, Kuo G, Weiner AJ *et al*. (1989) Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome *Science* **244**: 359–62) *J Hepatol* **36**: 582–5.

Researchers used large volumes of blood from an infected chimpanzee with a high level of infection to isolate the virus. Proteins in the chimpanzee blood were then screened against serum from a NANB hepatitis patient, which was expected to contain anti-NANB hepatitis antibodies. Eventually a NANB hepatitis viral protein in the chimpanzee blood was found to react with antibodies from the human patient, possibly due to the high levels of viral particles in the chimpanzee blood. With the genome available, it was possible to develop reliable diagnostic tests for what was subsequently termed hepatitis C. Treatment strategies have also been developed in animals although a vaccine does not yet exist.

6.26 The animals in the study described above could be expected to suffer symptoms similar to those experienced by humans, especially at high infection doses. According to the US National Center for Infectious Diseases, 80 percent of people with hepatitis C have little or no signs or symptoms, whereas others may experience jaundice, fatigue, dark urine, abdominal pain, loss of appetite, nausea and eventually chronic liver disease.[25] Additional implications for welfare relate to the long-term husbandry of the infected animals as they may be infectious to other animals and to humans, and must therefore be kept in single housing.

6.27 The major cause of hepatitis C infection was formerly blood transfusion.[26] It is now routine to screen donated blood for hepatitis C, which has vastly reduced transfusion-mediated infection in industrialised countries. The discovery and characterisation of the virus, its role as the etiological agent and the mechanisms whereby it produced disease in chimpanzees led to an understanding of the primary role of the virus in post-transfusion hepatitis and its tendency to induce persistent infection and chronic liver disease. Approximately 170 million people worldwide are chronically infected with hepatitis C,[27] many of whom will develop cirrhosis and liver cancer.

6.28 Because of the long asymptomatic period (up to 20 years), most infected people are unaware that they carry the virus and continue to be a source of new infections. Diagnostic assays to detect the virus are therefore essential to identify these patients. Current work on chimpanzees is not permitted in the UK, as the Home Office does not grant licences for research involving the great apes (see paragraph 13.6). Without the research described above, very little would be known about hepatitis C, and diagnostic tests would not be available. Many scientists believe that the lack of a reliable animal model other than the chimpanzee is the single greatest barrier blocking the development of a safe and effective vaccine.

## Study of polio and the development of polio vaccine

6.29 Animal disease models have been used in the study of poliomyelitis (polio), enabling an understanding of the disease process at the cellular level and facilitating the subsequent development of an effective vaccine. The polio virus enters the body through the mouth, from where it can travel to the digestive system and enter the bloodstream. The virus invades the CNS and destroys motor nerve cells, leading to paralysis and sometimes death. Before vaccines were introduced in developed countries in the late 1950s and early 1960s, polio was a common disease, estimated to be responsible for crippling more than half a

25 National Center for Infectious Diseases (2005) *Viral Hepatitis C*, available at: http://www.cdc.gov/ncidod/diseases/hepatitis/c/fact.htm. Accessed on: 26 Apr 2005.

26 Alter HJ, Purcell RH, Shih JW *et al*. (1989) Detection of antibody to hepatitis C virus in prospectively followed transfusion recipients with acute and chronic non-A, non-B hepatitis *N Engl J Med* **321**: 1494–500.

27 World Health Organization (2000) Fact sheet No. 164 *Hepatitis C,* available at: http://www.who.int/mediacentre/factsheets/fs164/en/. Accessed on: 26 Apr 2005.

million people around the world per year.[28] Since the introduction of vaccines, polio has largely been eliminated from industrialised countries.[29]

6.30 It had long been thought that polio was infectious, and in 1908 two researchers aimed to induce polio in several animals by injecting them with extracts of spinal cord material from a boy who had died of the disease. While the extracts did not cause polio-like disease in rabbits, guinea pigs or mice, the disease manifested itself quickly in Old World monkeys. Later, researchers were able to transmit polio from monkey to monkey by the injection of extracts of diseased spinal cord. Thus the virus could be propagated and an animal model of the disease was created. Use of this animal model in further studies led to the identification of the polio virus. Welfare implications for animals used in this early research extended over a broad range, but could be expected to resemble some of the symptoms experienced by humans.

6.31 In 1939, researchers were able to adapt one of the strains of the polio virus to make it infectious to mice, thus creating a more convenient rodent model for the disease. In the 1940s, researchers who were subsequently awarded a Nobel Prize demonstrated that the polio virus could be grown in cultured human cells, a property essential for future research on the virus. It was still not possible to observe the virus under the microscope at that time. Therefore, in order to confirm that the virus did propagate in cultured tissue, fluid was injected from the cultures into animals to observe if the disease developed.[30] In 1949, research on rodent models showed that there are in fact three types of polio virus.[31] In the 1950s Dr Jonas Salk used cultured monkey kidney cells to grow the virus. He then used the virus particles to produce the first vaccine which was found to be very effective at preventing the disease in humans, although people could still carry and spread the virus if it invaded their intestinal tract. In the 1960s, a new oral vaccine against the disease was developed. This vaccine contained live virus which had been 'attenuated', or weakened, by repeatedly growing it in cultured monkey cells. The vaccine produced an adequate immune response without causing an infection. The live attenuated virus, however, can sometimes revert to a virulent form and cause infection. Animals are currently used to test the potential virulence of each batch of vaccine that is produced to overcome the problem of occasional vaccine-associated poliomyelitis (see Box 8.5).

6.32 Mice and monkeys were used during important stages of the study of polio and the subsequent development of the vaccine. However, the initial development of the polio vaccine is regarded by some as an example which shows that animal research is misleading.[32] The early research was controversial because, in the first half of the 20th century, the dominant scientific theory was that the polio virus entered the body through the olfactory nerves of the nose, as indicated by experiments in monkeys. Scientists, particularly in the USA and Canada, inferred from these observations that it would be useful to develop prophylactic nasal sprays. The sprays were tested on animals and then on humans. In one large-scale trial in Toronto in 1937, the spray was tested on 5,000 children. The trial results soon revealed that the spray was ineffective as a preventative for infection by the virus and,

28 Eggers HJ (1999) Milestones in early poliomyelitis research (1840 to 1949) *J Virol* **73**: 4533–5.

29 The World Health Organization has recently estimated that polio would be eliminated during 2004–5, although similar statements have been made before. In 2003 there were 784 confirmed cases of the virus, mostly occurring in Africa and south-east Asia, particularly in Nigeria, India and Pakistan. See World Health Organization *Polio Eradication*, available at: http://www.polioeradication.org/; *Polio Case Count*, available at: http://www.who.int/vaccines/casecount/case_count.cfm. Accessed on: 26 Apr 2005.

30 For a mini-review of early polio research see Eggers HJ (1999) Milestones in early poliomyelitis research (1840 to 1949) *J Virol* **73**: 4533–5.

31 Current vaccines contain a mixture of the three types which together confer immunity.

32 See Paul JR (1971) *A history of poliomyelitis* (New Haven and London: Yale University Press).

furthermore, that the spray caused adverse reactions.[33] It was then discovered that humans are in fact primarily infected via the digestive system and not through the nose. The researchers had not fully understood the pathogenesis of the disease and wrongly assumed that viral entry was via the nose. Thus, this error does not support the claim that polio is an example showing that, in principle, animals are unsuitable models for the disease. Rather, it indicates that failures in this case resulted from a false hypothesis made by the researchers.

## Diseases for which treatments and cures have been difficult to develop

### *HIV/AIDS*

6.33 Mounting epidemiological evidence led to the recognition of the infectious nature of the HIV/AIDS disease in the early 1980s. Shortly after, it was demonstrated through studies with chimpanzees that the primary disease-causing virus, HIV-1, was transmitted in blood and blood products and body fluids. These findings revealed that national blood banks were at high risk of providing contaminated transfusions and transfusion products to patients. Widespread screening of blood supplies was quickly initiated. Two major groups of HIV viruses, termed HIV-1 and HIV-2, were identified, each consisting of a complex range of variants. As the virus replicates in infected people and populations, it generates natural variants that continuously escape and evade the human immune system. In addition, the complexity of the virus within each person depends on their own genetic makeup so that within a population of infected people there develops a large variety of different types of HIV. This rapidly evolving virus population is a 'moving target', and has become one of the major scientific obstacles facing the medical research community. The virus also has complex interactions with a number of different types of cells within the body, particularly those that have a primary role in the immune system. For these reasons it has not yet been possible to develop a vaccine or effective means of ridding the body of the virus.

6.34 An ideal animal model for HIV-1/HIV-2 infection would have the following features: practicalities such as ease of handling and housing of the animals, a well-characterised physiology and immunology, and readily available species-specific reagents. It would also need to be susceptible to the form of HIV-1 that causes HIV/AIDS in humans or a very closely related virus. The model would require similar routes of infection and target cells, and should develop similar symptoms to those of the human disease.[34]

6.35 However, no single ideal animal model perfectly reproduces the symptoms of HIV-1 infection and development of the disease in the diverse human population. The primate models that are currently available have inherent limitations.[35] Despite the fact that chimpanzees are naturally infected with the virus SIVcpz, which is the most likely forebear of HIV-1 in humans, they are resistant to AIDS. Some macaque species are infected by an HIV-2-related lentivirus called SIVsm, which causes a form of AIDS that closely resembles the human disease. In addition, rhesus macaques are outbred like the human population, and have a similar spectrum of disease outcomes. But while similarities with humans and cross-reactive immunological reagents exist, the current human epidemic is predominantly caused by HIV-1 and therefore the model does not provide all the features needed. More recently, GM rodents engineered to express human receptors on their cells have provided replacements for primates in certain experiments.[36]

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33 Rutty CJ (1996) The Middle-Class Plague: Epidemic Polio and the Canadian State, 1936-1937 *Can Bull Med Hist* **13**: 277–314.

34 Adapted from Lewis AD and Johnson PR (1995) Developing animal models for AIDS research – progress and problems *Trends Biotechnol* **13**: 142–50.

35 Lewis AD and Johnson PR (1995) Developing animal models for AIDS research – progress and problems *Trends Biotechnol* **13**: 142–50.

36 For example, see the description of research at the Biomedical Primate Research Centre, available at: http://www.bprc.nl/BPRCE/L4/AltRep.html. Accessed on: 27 Apr 2005; Van Maanen M and Sutton RE (2003) Rodent models for HIV-1 infection and disease *Curr HIV Res* **1**: 121–30.

6.36 Scientists have developed a hybrid virus SIV/HIV-1, termed SHIV, which infects rhesus macaques. This allowed the replacement of chimpanzees with a new model for the research into the HIV-1 disease and potential vaccines. Although some progress has been made in understanding the disease, the HIV/AIDS disease is rapidly changing. The viral variants that are engineered and used in the laboratory are often outdated before they are evaluated against new vaccine candidates.[37]

6.37 The first two Phase III clinical trials of vaccines in humans have recently failed.[38] The strategy pursued was one that had originally seemed effective in a laboratory setting using chimpanzees in the late 1980s and early 1990s. While it is important to consider this example as a possible failure of an animal model to predict the outcome in humans, scientists also assert that it is imperative to closely examine the data and the interpretations made from these studies. It proved possible to protect chimpanzees vaccinated with HIV-1 vaccine strains from closely related viral variants. But when tested in humans, the vaccines were exposed to an extremely wide variety of HIV-1 variants circulating in the population.[39] It could therefore be concluded that the failure was primarily a result of invalid extrapolation of data and/or the use of an untested hypothesis by the investigators before proceeding to Phase III clinical trials.[40]

***Cancer***

6.38 Cancer encompasses a wide range of complex and different diseases of many different cell types and organ systems, characterised by uncontrolled cell division and abnormal tissue growth. Some forms of cancer are genetically inherited, others are caused by the environment, viral infections or chronic inflammation. Some affect the young whereas others more commonly emerge late in life. Animal research has contributed to many advances in the treatment of cancers, and in contrast to the situation 25 years ago, some cancer types are now largely curable diseases. Nevertheless, cancer remains a leading cause of death in developed countries, and it has been observed that research progress has been slow despite the extensive use of animal models.

6.39 Many animal models in cancer are provided by various strains of rodents. There have been difficulties in translating cancer treatments that are effective in rodents (mostly mice) to humans. This is commonly due to genetic, physiological and immunological differences between the mouse and humans. Primate models of cancer are rare, expensive and the animals are difficult to handle and house. Thus, there is a large gap between 'proof of concept' studies in mice and an effective therapy in humans. With a lack of primate models, the genetic differences which remain between humans and mice mean that therapies developed in mice cannot be moved with any confidence to the clinic. The translation of observations from basic research in the laboratory to human cancer trials has often been a slow and disappointing process. Nonetheless, there have been some notable successes such

37 In addition, evidence now indicates that the HIV-1 epidemic is having an impact on the genetics of the human population that is most heavily affected by the epidemic, thus further increasing the complexity.

38 Cohen J (2003) AIDS Vaccine Trial Produces Disappointment and Confusion *Science* **299**: 1290–1; Cohen J (2003) AIDS Vaccine Still Alive as Booster After Second Failure in Thailand *Science* **302**: 1309–10.

39 Klausner RD, Fauci AS, Corey L *et al*. (2003) Enhanced: The Need for a Global HIV Vaccine Enterprise *Science* **300**: 2036–9.

40 See also Lemon R, Dunnett SB (2005) Editorial: Surveying the literature from animal experiments BMJ 330: 977-978. The authors comment on reviews which claim that animal research frequently fails to prevent problems which arise in later trials in humans, or once a medicine has been marketed. They refer to a case given to support this view, in which problems arose in human trials of a post-stroke treatment involving the calcium channel blocker nimodipine. They observe that the example is not suited to support a lack of scientific validity of animal research in this area, as the researchers conducting the nimodipine trials failed to take into account publications which showed that the medicine had deleterious effects in animal experiments. The authors highlight the importance of ensuring that all relevant results from animal research are reviewed before commencing a clinical trial of a new treatment, and that care needs to be taken to avoid that scientific, commercial or personal pressures lead to an inappropriately narrow selection of evidence.

as tamoxifen for the treatment of breast cancer and goserelin for prostate cancer, both developed using experiments in rats and mice.

## Summary

6.40 Certain animal models have played significant roles in the study of particular diseases and have led to the development of effective interventions. For RA, polio and hepatitis C successful treatments. In the case of TSEs, animal models have been essential for increasing our understanding of the nature of the diseases and in the development of public health measures to limit their spread. The animals involved in this type of research usually suffer from the characteristic symptoms of diseases such as hepatitis C, RA or scrapie. Where possible, animals are euthanised at humane endpoints, although this may not always be the case if the long-term implications of the disease are under study.

6.41 We have also noted that certain animal models of human disease have their limitations, and that there are examples where treatments that are effective in animal models fail to have the same effect in humans. This is primarily because of the complex pathogenesis of diseases such as HIV/AIDS and cancer which have many different sub-types in humans and animals. Scientists involved in this type of research believe that further refinement of models that are more closely related to humans, especially primate or GM animal models, may accelerate the process.

6.42 The research summarised here has provided significant knowledge about disease processes and helped to identify strategies for interventions. Although the development of treatments for some cancers has been slow, there have also been successes in the case of breast and prostate cancer. Knowledge about basic biological processes in other forms of the disease has increased. Such insights are likely to improve understanding of similarities and differences in disease processes in humans and animals which may contribute to increasing knowledge about the development of preventatives and cures. Similarly, the failure to develop a fully effective cure or treatment for specific diseases, especially for complex multisystem diseases such as AIDS, does not by itself imply that existing animal models are generally invalid. Rather, these observations should invite reflections on how research methodology and existing animal models can be improved.

# Chapter 7

## Genetically modified animals in the study of human disease

# Genetically modified animals in the study of human disease

## Introduction

7.1 In Chapter 5 we gave an overview of the many ways in which animals are used for basic research, including genetic modification (see paragraphs 5.16–5.23). In Chapter 6 we focused on their use as disease models. We now consider an area which brings together GM animals and the study of human disease. In this chapter we first explain the general relevance of drawing on genetic data for the purposes of both improving our understanding about disease processes, and devising ways of preventing and treating them. We then describe commonly used disease models and explain how and why mice, zebrafish and rats are used in this type of research. We also give a range of examples that illustrate the scientific benefits and welfare implications for GM animals involved in research.

7.2 The pathology of all diseases, be they infectious, inherited or environmentally induced, is affected either directly or indirectly by an individual's genome. The study of genetics can help us to understand these fundamental interactions. The recent sequencing of the human and mouse genomes has revealed remarkable similarities. Ninety-nine percent of the genes in these two genomes have direct counterparts in the two species, although they have slightly different structures and functions, and are in some cases regulated differently. Because of these similarities and because of practical considerations (mice breed rapidly, and methods of genetic modification are more effective, when compared with other mammals) the mouse is used as a model for research on human diseases in a range of different types of studies.

### Comments on the use of GM animals in the study of human disease from respondents to the Consultation

'The use of genetically modified animal models has allowed researchers to generate more accurate and appropriate models of human diseases. This has facilitated progress and makes it more likely that research will transfer to human subjects more quickly.'
*Genetic Interest Group*

'One viewpoint is that the use of transgenic animals will result in a reduction of the use of larger animals…as rodent models for disease are now available.'
*Sarah Johnson, member of the ethical review panel at the MRC NIMR*

'Many GM animals have normal lifespans and suffer no ill effects as a result of the presence of a transgene. Some GM animals do suffer as a result of their genetic modification but…in many cases this is less than the alternative methods of generating a similar 'model' through surgery or chemical treatment.'
*Anonymous*

'The number of GM animals we use is rising fast. This process is best described as commodification. The moral problem is that animals are not computers or areas of land or other "resources".'
*Shaun Carey*

'Even when scientists think they have a "good model" it is difficult to determine how much its attributes are due to its genes or to environmental factors. Wildly differing results have been found to occur in different laboratories using the same strains of animal in the same procedures.'
*Animal Aid*

'GeneWatch believes that an unjustified emphasis is being placed on the potential for GM animals to help understand and treat disease. This is driven by a lack of recognition of the complex nature of most diseases and the failings of laboratory research to mimic environmental, social and economic factors in disease.'
*GeneWatch UK*

7.3 Naturally occurring animal models of human genetic diseases are rare, probably because such animals fail to survive in the wild. In GM models, detailed analyses of the development, physiology and biochemistry of a particular disease can be related to a specific gene or group of genes. It then becomes possible to understand the often complex relationship between the gene(s) and the disease process. Furthermore, comprehensive genomic analysis can improve not only our understanding of basic biological processes but also help us appreciate the potential of genes to affect disease processes. It is also possible

to insert human genes into the genome of mice to study, for example, their physiological role. Researchers working in the field believe that, in some cases, such experiments may yield more accurate animal models of human disease (see paragraph 6.35).

7.4 The animals that are used most frequently to model the genetics of human disease are the mouse, rat and zebrafish. Virtually all of the GM animals used in experimental procedures in the UK during 2003 were from this group (see Appendix 2).[1] As we explain in more detail below, these three organisms have been chosen for a variety of reasons.

## The mouse as a model for human disease

7.5 The genetic modification of organisms such as the fruit fly *Drosophila*, the nematode worm *C. elegans*, yeast, bacteria and viruses can provide useful information on the fundamental biological role of genes. However, studies in these species cannot address questions that concern the effects of gene modification on the development of organs or physiological disease processes that are only found in vertebrates or mammals. The mouse is therefore increasingly the preferred organism for modelling the genetics of human disease. It is difficult to make an accurate current estimate of the total number of mouse mutant lines available in the world today but estimates suggest that there are more than 3,000.[2] There are several approaches that are routinely used for manipulating the mouse genome and generating new GM mice, including:

- gene targeting by using ES cells (see paragraph 5.6);
- a mutagenesis programme using chemical mutagens followed by screening to identify relevant disease models (see paragraph 5.18); and
- new approaches, including the use of technologies to inactivate the RNA transcript of a gene so that it cannot be translated into a protein (RNA interference, or RNAi).

Depending on the method used to produce mutations (see paragraphs 5.17–5.22), the number of mice that are required to establish a line carrying a specific mutation varies from about 50 animals to several hundred. Additional animals will be required to investigate the phenotypic effects of any scientifically useful mutant that is created. Many large-scale research programmes involving these techniques are in progress at a number of centres around the world. One of the aims of the international community of mouse geneticists is to develop at least one mouse mutant line for every gene in the mouse genome over the next 20 years. The total number of mice that are expected to be used in mutagenesis and phenotyping studies is of the order of several million each year in the UK alone (see paragraph 5.22).[3]

7.6 This use of GM animals for the study of human disease is rapidly expanding both in capacity and sophistication. A number of 'mouse clinics' are being built around the world with the space and tools to begin the analysis of the many thousands of mouse lines that will be developed. Ultimately, it is expected that highly detailed data that relate mutations in genes to different disease processes in the animal will be generated.

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1 GM animals were used in a total of 764,000 regulated procedures in 2003 (see paragraph 13.25). This figure comprises 27 percent of all procedures for 2003. Ninety-eight percent of the procedures using GM animals involved rodents. Sixty-eight percent of the total number of GM animals were used for the maintenance of breeding colonies but not for any further procedures. See Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (London: HMSO).

2 Abbott A (2004) Geneticists prepare for deluge of mutant mice *Nature* **432**: 541

3 For further information, see The Comprehensive Knockout Mouse Project Consortium (2004) The Knockout Mouse Project *Nat Genet* **36**: 921–4.

7.7 The question arises as to how relevant the information on disease processes in mutant animals, especially the mouse, will be to the genetics of disease processes in humans. There are a number of contrasting points to consider:

i) Comparative anatomy and comparative pathology represent long-established traditions that have made significant contributions to the general understanding of the function of mammalian systems, and therefore to the understanding of disease processes in both humans and mammals. The scientific community also uses genetic models to provide valuable comparative physiological, developmental, biochemical and pathological information across species.

ii) The major differences in the one percent of mouse genes that do not have direct counterparts in humans (see paragraph 7.2) are accounted for by specialist classes of multigene families. These mouse-specific clusters often correspond to only a single gene in the human genome. Most clusters involve genes related to reproduction, immunity and the ability to smell (olfaction). One example is a group of genes in the mouse that is called the vomeronasal receptor family and plays a specialist role in mouse reproduction. In humans, this structure is non-functional.

iii) In evolutionary terms, the mouse and human diverged some 80 million years ago, which explains the significant differences in some areas of their comparative physiology including, for example, longevity and many behavioural adaptations. While there is a very high concordance of genes between the two genomes, it is generally agreed that differences between humans and mice are due to changes in the patterns and timing of gene expression. These changes reflect alterations in the regulation of genes that have occurred since the two species diverged.

7.8 Clearly, the mouse is not a replica of a human, but biomedical scientists maintain that the similarities are sufficient to make informative comparisons. They also take the view that, although the effects of mutations in genes in the mouse might not replicate exactly the effects that they exert in humans, they can provide a robust guide to the function of genes in mammalian species. Given that a large number of mouse mutations is already available, what is the evidence that there have been useful contributions to our understanding of human disease genetics? In the next section we give examples of specific disease models to address this question.

## Disease models in the mouse

7.9 Gene dysfunction is at the root of all genetically determined disease processes. Not all gene dysfunctions are heritable as gene expression is also influenced by injury, infection, ageing, cancer, neural degeneration and neural regeneration. By asking how often mouse mutants reproduce the effect of mutations in the corresponding human gene, it is possible to assess the utility and relevance of disease models. We illustrate this below with several examples (see also Table 7.1), which also show that the implications for the welfare of animals involved in such research are wide ranging.

i) **Diabetes:** Mutations in the glucokinase gene in humans lead to a form of type II diabetes[4] that manifests itself in the young, called maturity-onset diabetes of the young (MODY). Mutations in the glucokinase gene in the mouse also develop a type II diabetes, very similar to that seen in human MODY patients.[5] These mutants provide a useful model of

4 Type II diabetes is a late-onset disease that is not necessarily life-threatening and which does not always require control with insulin administration.

5 Toye AA, Moir L, Hugill A *et al*. (2004) A New Mouse Model of Type 2 Diabetes, Produced by N-Ethyl-Nitrosourea Mutagenesis, Is the Result of a Missense Mutation in the Glucokinase Gene *Diabetes* **53**: 1577–83.

MODY and enable scientists to investigate the relationship between mutations in the glucokinase gene and the pathogenesis and severity of the disease. Some of the mouse strains carrying mutations in the glucokinase gene have normal viability and fecundity and there do not appear to be detrimental effects on welfare. Other mutations, however, lead to more severe effects and are lethal during embryonic development.

ii) **Deafness:** *The shaker1* mouse mutant displays a profound hearing loss and was one of the first mouse mutants investigated as a model of human genetic deafness at a time when little was known about the disorder. Researchers identified the mouse gene underlying the *shaker1* mutant and then located the corresponding gene in the human genome. It was found that the *shaker1* locus was encoded in mice by a gene of the type called myosin VII.[6] It was subsequently demonstrated that mutations in the myosin VIIA gene in humans lead to hearing loss. Some of the mutations in this gene in humans can also lead to a syndrome where there is both hearing loss and blindness at around seven or eight years of age, due to the condition retinitis pigmentosa. Yet none of the myosin VIIA mutations isolated in the mouse cause blindness, even in very old mice. This may be a reflection of the short lifespan of the mouse which prevents the retina from receiving sufficient exposure to light to elicit pathological changes. Nevertheless, they do, as the name suggests, show hyperactivity, head-tossing and circling activity in addition to hearing loss.[7]

iii) **Psychiatric disorders:** It is probable that the equivalent conditions of many human psychiatric disorders are not exhibited in mice because of differences in the brain structures between the two species. It is also the case that many of the human patients who suffer from these disorders do not inherit them through simple genetic determinants, and that environmental factors play an important role. Scientists are exploring the role of the genes involved in certain inherited psychiatric disorders by examining their function in the mouse, and their influence on other genes and neurotransmitter systems at the level of neurones and the brain. Understanding how these genes function is important for the development of new therapies, although the modification of relevant genes in mice may not necessarily create the neuropsychiatric effects that are exhibited in humans.[8]

Mutant mice have also been screened for subtle behavioural changes to help identify genes that may be implicated in complex behavioural disorders in humans, such as anxiety or schizophrenia.[9] Mice carrying mutations that affect behaviour rarely, if ever, manifest serious welfare problems, although there may be loss of complex subtle behaviours that may be revealed only in the wild or in response to complex stimuli that are not usually available to mice in the laboratory.

iv) **Neurodegenerative disorders:** Few neurodegenerative disorders, such as Parkinson's disease and Alzheimer's disease, are linked to single gene mutations. In Parkinson's disease, three important mutations in genes responsible for different cellular functions (alpha-synuclein, parkin and a ubiquitin hydrolase) have already been identified. Three different genes with mutations implicated in Alzheimer's disease (beta-amyloid, presenilin and tau) have also been described. Reproducing the human form of these mutated genes in mice produces comparable pathologies to those in humans. Although

6 Gibson F, Walsh J, Mburu P *et al*. (1995) A type VII myosin encoded by the mouse deafness gene shaker-1 *Nature* **374**: 62–4.

7 Gibson F, Walsh J, Mburu P *et al*. (1995) A type VII myosin encoded by the mouse deafness gene shaker-1 *Nature* **374**: 62–4.

8 Seong E, Seasholtz AF and Burmeister M (2002) Mouse models for psychiatric disorders *Trends Genet* **18**: 643–50.

9 Ohl F and Keck ME (2003) Behavioural screening in mutagenised mice: In search for novel animal models of psychiatric disorders *Eur J Pharmacol* **480**: 219–28.

there is not yet a model which contains all of the relevant features that characterise the pathology of Alzheimer's disease, the models available are nevertheless of great interest to researchers.[10] A variety of approaches, including histopathological, imaging, electrophysiological and molecular genetic techniques have been particularly helpful for mapping the progression of neurodegenerative disorders in mouse models as well as determining the effects of several of the mutations.

With regard to welfare implications, mouse models of neurodegenerative disease may show a variety of neurological impairments including, for example, tremors and ataxia (loss of full control of bodily movements). These symptoms often have significant effects on fecundity and viability and require careful monitoring. The diseases may also affect a mouse's ability to interact with other animals, and to carry out behaviours such as play, running and climbing.

v) **Lesch–Nyhan disease:** Mutations in the *Hprt* gene, which encodes an enzyme involved in metabolism (hypoxanthine-guanine phosphoribosyltransferase), lead to a rare but very severe neurological syndrome in humans known as Lesch–Nyhan disease, the most characteristic feature of which is self-destructive biting. One of the earliest targeted mutations developed in the mouse, applying the reverse genetic approach (see paragraphs 5.19–5.22), resulted in the disruption of the *Hprt* gene. However, *Hprt* mouse mutants show none of the phenotype characteristics of Lesch–Nyhan syndrome. Researchers found that in the mouse an alternative enzyme pathway ameliorated the effect of the *Hprt* mutation, and obvious adverse effects on animal welfare from the generation and study of the mutant model have not been detected.

vi) **Cancer:** Prior to the sequencing of the mouse genome, investigating spontaneous mutations in genes involved in cancer required approximately 1,000 mice for cross-breeding in order to map a gene to a specific chromosomal region. This region would usually contain several genes, all of which needed to be sequenced to determine which one contained the mutation. As a result, it would have taken 15 years to identify ten possible genes that were involved in cancer, whereas this step can now be achieved in months. Moreover, comparisons between the mouse and human genomes help researchers to find related human genes encoding proteins that could be candidates for the development of new medicines. The recent development of a library of some 60,770 full-length cDNAs[11] provides researchers with a functional copy of every mouse gene that can be readily genetically modified.[12] This library is especially useful for studying human cancers or the role of other human genes involved, where the identity and location of the mouse homologue is unknown. With regard to animal welfare, mouse models of cancer usually demonstrate an increased incidence of tumours and an increased morbidity that will require careful monitoring.

7.10 In assessing the usefulness, relevance and validity of the large amount of data that are already available from studies of GM mice, advocates note that it is important to consider a number of features that characterise the investigation of mouse models, and which apply more generally to the analysis of any genetic animal model of human disease:

10 See, for example, Lee VM, Kenyon TK and Trojanowski JQ (2005) Transgenic animal models of tauopathies *Biochim Biophys Acta* **1739**: 251–9.

11 Complementary DNA: DNA produced from RNA sequences, which means that it contains only the sequences that code for proteins.

12 The number of mouse cDNAs identified greatly exceeds the number of genes as some do not in fact code for proteins. See Suzuki M and Hayashizaki Y (2004) Mouse-centric comparative transcriptomics of protein coding and non-coding RNAs *Bioessays* **26**: 833–43.

- First, when investigating and understanding the mechanistic basis of disease, as with all comparative analyses, the differences may be as instructive as the similarities. This is a feature that pervades not only comparative genetics but also comparative anatomy, physiology and pathology.
- Secondly, all or some of the relevant features of the phenotype arising from any mutation may not be detected by the methods commonly used. Some mutations do not result in any observable consequence. This may be due to: (i) the difficulty of detecting very subtle phenotypes; (ii) the effects of 'genetic background' that may modify the phenotypic outcome (see below); and (iii) the redundancy of pathways involved in biological systems.[13] The lack of a phenotype may provide relevant information about the genetic pathways involved in any disease process but negative results often go unreported in the scientific literature.
- Thirdly, the disease phenotype resulting from a mutation may be modulated by the person's genetic makeup. For example, while all siblings in a family might carry a mutation, they may vary in the way in which other genes in their genome affect the manifestation of the disease.[14] As we have said, it is similarly true that the effect of mutations in mice can be very significantly altered by their genetic background. Analysis of the mouse genome allows researchers to better understand these interactions and to identify other genes that modify the effects of a particular mutant gene, further elaborating the understanding of the genetic mechanisms of disease.
- Fourthly, scientists do not expect a mutant model to replicate the entire complexity of the process of human disease. This is particularly true in the development and analysis of neurological and neurobehavioural disease models (see paragraph 7.9 (iii)). Rather, the aim is to identify genes that are involved in specific facets of complex neurobehavioural processes, which are called *endophenotypes*. Study of the separate components in the model system can help to improve understanding of the complexity of the phenotype.
- Finally, the outcomes for animal welfare are very variable, ranging from no immediately noticeable effects to significant effects on welfare and morbidity. They are also very unpredictable (see paragraph 4.57).

In conclusion, mouse models require careful analysis in order to assess their relevance and effects (see Table 7.1). While some animal protection groups remain sceptical about their overall usefulness,[15] scientists working in the field maintain that, provided the points above are appropriately considered, their use produces significant information concerning the function of genes in mammalian disease processes and human genetic disease.

13 (iii) 'Redundancy' refers to the fact that biological systems do not always fail due to the lack of a particular enzyme, for example, as another pathway may compensate (see paragraph 7.9 (v)).

14 There may also be environmental effects such as air pollution or exposure to certain chemicals in the workplace which may influence the expression of the disease phenotype.

15 British Union for the Abolition of Vivisection (2002) *Designer Mice* (London: BUAV).

## Table 7.1: A summary of the contribution and limitations of GM mouse models in leading areas of disease research

| Disease area | Mouse models | Outcome and limitations |
|---|---|---|
| Diabetes | Mutants available including type I and type II diabetes models (see paragraph 7.9 (i)). | Insights into genetic pathways involved in diabetes and the hormonal and metabolic control of blood sugar. |
| Obesity | Mutants available that contribute to obesity under a variety of conditions.[16] | Fundamental insights into the hormonal (leptin) and hypothalamic pathways of obesity have been obtained through the use of mouse models and newly engineered mutants. |
| Neurological | Mutants available that affect neuronal growth, differentiation and plasticity.[17] | Significant new information on genes involved with the development of neuronal processes. This knowledge is important for the development of therapeutic approaches to neurological disease. |
| Neurobehavioural | Mutants available that affect a number of endophenotypes (see paragraph 7.10) of more complex behavioural processes, including: circadian rhythms, learning and memory, anxiety, feeding, sexual behaviour, aggression and maternal care. | None of the available mutants are true models of the complex behavioural outcomes of psychiatric disease in the human population (see paragraph 7.9 (iii)). |
| Sensory | Mutants available that affect both hearing and vision (see paragraph 7.9 (ii)). | Significant insights into the genetics of deafness in the human population. While there are many useful models of retinopathies in the mouse, the short lifespan of this species may restrict its usefulness for studying some aspects of retinal degeneration. |
| Cardiovascular | Several mutant models available.[18] | Some progress, for example, in the study of atherosclerosis through the use of apoE mutants. However, progress in GM models has been slow and has only just begun to accelerate. Until recently, the rat was a preferred model for studying hypertension and other cardiovascular phenomena. |
| Cancer | Mutants and strains of mice which show significant variation in both frequency and types of cancer (see paragraph 7.9 (vi)). | Historically, a focus of GM mouse research. While the formation of tumours in the mouse does not always mirror that in humans, many insights into the role of genes that are responsible for causing cancer in mammals have been gained. |
| Musculoskeletal | Many myopathy models;[19] but fewer GM mutants available that model human bone disease. | Mouse models have provided insights into the genes involved with myopathies in the human population. These mutants have been crucial to developing a better understanding of myopathic processes in humans and in the assessment of potential therapies. |
| Ageing disorders | Mutants available for Alzheimer's and Parkinson's disease (see paragraph 7.9 (iv)). | Considerable progress has been made in understanding Alzheimer's disease, Parkinson's disease and other neurodegenerative disorders. Receptors that could act as targets for future new drugs have been identified. |

16 See Carroll L, Voisey J and van Daal A (2004) Mouse models of obesity *Clin Dermatol* **22**: 345–9.

17 Usera PC, Vincent S and Robertson D (2004) Human phenotypes and animal knockout models of genetic autonomic disorders *J Biomed Sci* **11**: 4–10.

18 Takahashi N and Smithies O (2004) Human genetics, animal models and computer simulations for studying hypertension *Trends Genet* **20**: 136–45.

19 See Shelton GD and Engvall E (2005) Canine and feline models of human inherited muscle diseases *Neuromuscul Disord* **15**: 127–38.

## Zebrafish and rats as disease models

7.11 Both the zebrafish and the rat play a role as disease models in the investigation of the genetics of human disease. Each occupies a narrower niche than the mouse for several reasons.

### *Zebrafish*

7.12 There has been a very significant increase in the use of zebrafish for the study of disease processes in humans. Zebrafish reproduce easily and quickly and have morphological and physiological similarities to mammals. Those who study zebrafish hope that use of the species will lead to progress in several aspects of the drug development process, including target identification, disease modelling, lead discovery and toxicology (see paragraphs 8.6–8.16).[20] The study of the zebrafish genome is relatively well advanced and a complete genome sequence will soon be available.[21] It has been the focus of several major forward genetic screens (see paragraphs 5.17-5.18) for a variety of diseases and other phenotypes. Zebrafish models have been developed for several human diseases, including blood disorders, diabetes, muscular dystrophy and neurodegenerative diseases.[22] The transparency of the developing zebrafish embryo has enhanced its usefulness for studying the genetics of development. One area where much progress has been made is in the study of the genetics of the development of the heart and vascular system. Increased understanding about the genes involved has also contributed to understanding of these processes in vertebrates.

### *Rat*

7.13 Research involving the rat has for many years lagged behind that of the mouse in terms of developing the techniques for manipulating its genetic systems. This, coupled with the expense of producing mutations in the rat, has been the primary reason for it having been used less widely than the mouse for the study of the genetics of disease processes. Although a complete genome sequence has recently been published,[23] the relative lack of tools for forward and reverse mutagenesis (see paragraphs 5.16-5.20) in the rat will continue to limit its utility. Nevertheless, several inbred rat lines have been developed. Many of these have been characterised for diseases such as diabetes and hypertension for which the rat is a particularly tractable model. Rats are the preferred species for these diseases because their large size is more suitable for the use of the technologies available for the measurement of phenotypes such as blood pressure. Comparisons between inbred lines have revealed a significant amount of variation in disease phenotypes. Genetic crosses between them show significant phenotypic differences and allow the genetic regions involved to be mapped and ultimately identified. For example, the genetics of hypertension is a major area for study in the rat and a number of genes have been identified that are involved in determining blood pressure.[24]

20 Zon LI and Peterson RT (2005) *In vivo* drug discovery in the zebrafish *Nat Rev Drug Discov* **4**: 35–44.

21 It is expected that the zebrafish genome sequence will be provided by the end of 2005. See The Wellcome Trust Sanger Institute (2005) *The Danio Rerio Sequencing Project*, available at: http://www.sanger.ac.uk/Projects/D_rerio/faqs.shtml#factsnine. Accessed on: 28 Apr 2005.

22 Rubinstein AL (2003) Zebrafish: from disease modeling to drug discovery *Curr Opin Drug Discov Devel* **6**: 218–23.

23 Gibbs RA, Weinstock GM, Metzker ML *et al*. (2004) Genome sequence of the Brown Norway rat yields insights into mammalian evolution *Nature* **428**: 493–521.

24 Herrera VL and Ruiz-Opazo N (2005) Genetic studies in rat models: insights into cardiovascular disease *Curr Opin Lipidol* **16**: 179–91.

## Summary

7.14 This chapter has described the use of GM animals in the study of human disease. The vast majority of animals that are genetically modified for this purpose are mice, rats and zebrafish. Although an animal model cannot be considered as an exact replica of a human disease, scientists working in the field have found that there are often sufficient similarities to make informative comparisons. Even when animals do not present disease symptoms that are similar to those of humans, useful information may still be discovered regarding gene function. For example, individual genes can be identified that are involved in specific facets of even complicated disease processes.

7.15 The number of animals required to establish an individual genetic line carrying a particular mutation currently ranges from 50 to several hundred. Over the next 20 years, a major increase in the production of GM animals is expected. The total number of mice used in mutagenesis and phenotyping studies in the UK is likely to be of the order of several million each year.

7.16 As with all animals kept in laboratories, the welfare of GM animals depends to a considerable degree on non-experimental conditions such as housing and handling. Specific issues relating to the way the animals are produced may be raised because of the large numbers involved. Care needs to be taken to create environments that are appropriate for the animals with regard to their basic species-specific needs, particularly concerning space, enrichments and interactions with other animals. Welfare issues may also be raised by the particular genetic modification. These may be severe if the animals are affected by, for example, a neurodegenerative disease. We have also described genetic modifications that have yielded useful results with regard to human disease but which do not appear to produce adverse effects on animal welfare. The main problems in assessing the welfare of GM animals are that (i) in most cases of forward or reverse genetic screens, the implications for welfare cannot be predicted (see paragraph 4.57); and (ii) it can sometimes be difficult to detect and measure more subtle adverse welfare effects (see paragraphs 4.3-4.7, 4.18 and 7.10).

# Chapter 8

## The use of animals for research in the pharmaceutical industry

# The use of animals for research in the pharmaceutical industry

## Introduction

8.1 The pharmaceutical industry conducts or supports approximately one third of the animal research that is undertaken in the UK. Some of this is basic research that seeks to examine normal biological processes and the nature of disease (see also Chapters 5 and 6). However, most has more specific, applied objectives and concerns the development of new medicines or vaccines, improved diagnosis or better methods of toxicity testing. Since the process of producing medicines has changed significantly over time, we begin with a brief overview of developments from the late 19th century to the present. We then describe the way medicines are currently produced in terms of eight stages. These are: discovery and selection of compounds that could be effective medicines (stages 1 and 2), characterisation of promising candidate medicines (stages 3 and 4), selecting candidate medicines and ensuring their safety (stage 5), clinical studies on humans (stages 6 to 8), and also research carried out to support the medicine once it has been marketed. For each stage we describe the way in which animals are used in the process, and give some examples of specific experiments. As in the case of research described in the previous chapters, welfare implications for the animals involved in pharmaceutical research are as diverse as the types of research and must be considered on a case by case basis. In this chapter we focus on the use of animals on the development of medicines for use in humans. We also consider briefly vaccines[1] and veterinary medicines.

## The development of the pharmaceutical industry

8.2 The modern pharmaceutical industry has its origins in the chemical industry of the late 19th century and the first half of the 20th century. A first peak of research activity concerned the development of treatments for war injuries and infectious diseases arising from mass migrations during and after the First World War. During the Second World War and subsequently, a much more systematic approach to the discovery of new medicines led to a significant increase in both medical discovery[2] and industrial activity.[3]

8.3 Early pharmaceutical research drew on existing animal models that were used in experimental physiology, extending established scientific traditions of using animals in research. New potential medicines were not directed at a specific target such as a cell receptor, as they are today. Rather, the effect of medicines was measured in relation to the general physiological response of an animal, such as changes in blood pressure. This method of screening for potentially beneficial effects of medicines used large numbers of animals, and was inefficient and cumbersome. As pharmaceutical research expanded in the 1950s and 1960s, the use of animals expanded in parallel. In the 1980s, novel techniques, improved facilities, computer technology and new materials became available and were integrated into the research and development process. The use of alternatives to solely animal-based research and development, such as cultured cells, also expanded.

1 See World Health Organization (2003) *State of the Art of New Vaccines: Research and development* (Geneva: WHO), available at: http://www.who.int/vaccine_research/documents/en/stateofart_excler.pdf. Accessed on: 29 Apr 2005.

2 HistoryWorld *Combined Medical Timeline (Wellcome Trust)*, available at: http://www.historyworld.net/timelines/timeline.asp?from=existing&D=1925&selection=&tid=yocb&title=Combined%20Medical%20Timeline&back=existing.asp. Accessed on: 26 Apr 2005.

3 Corley TAB (1999/2000) *The British Pharmaceutical Industry Since 1851*, available at: http://www.rdg.ac.uk/Econ/Econ/workingpapers/emdp404.pdf. Accessed on: 26 Apr 2005.

8.4 From the late 1980s these developments continued to transform pharmaceutical research and development. Information technology became more efficient, allowing the integration of rapidly expanding amounts of data generated by advances in basic biological knowledge. This information was integrated with data from new technologies such as high-throughput chemistry and biology, genomics, pharmacogenetics, advanced diagnostic imaging and the application of bioinformatics. Since the 1980s, the continued expansion of pharmaceutical research in the UK has also been accompanied by the increasing use of a wide range of modern methods, which we describe below (see Figure 8.1).[4] The use of these methods was one factor that contributed to the decrease in animals involved in commercial research during the same period, from 60 percent (or 2.1 million) of the total number of procedures in 1987, to 36 percent (or 1 million) of the total in 2003.[5]

**Capture the potential of the human genome industrialisation of drug discovery**

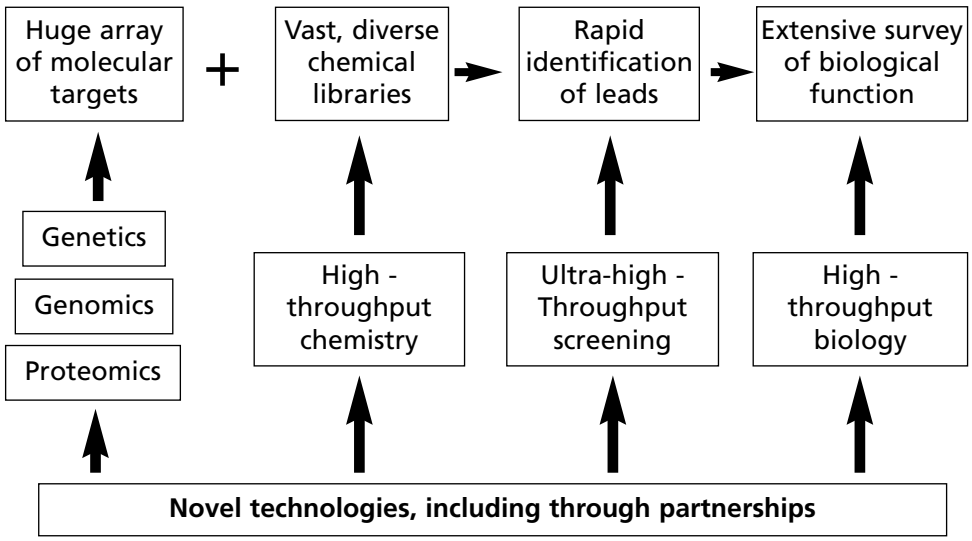


**Figure 8.1: The industrialisation of drug discovery to capture the potential of knowledge of the human genome**

Source: GlaxoSmithKline

## Use of animals in current pharmaceutical research and development

8.5 The discovery and development of new medicines[6] entails a very complex range of different methodologies (Figures 8.1 and 8.2). The process, undertaken primarily by the pharmaceutical industry, takes an average of 10–15 years.[7] In this section, we describe it in terms of eight stages,

4 The Association of the British Pharmaceutical Industry (ABPI) *The Development of Medicines*, available at: http://www.abpi.org.uk//publications/briefings/Dev_Medicines.pdf. Accessed on: 26 Apr 2005.

5 This figure includes the use of animals by companies outside of the pharmaceutical sector, for example in toxicity testing and ecotoxocity testing of products that might have an impact on the environment. See Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (London: HMSO), p22. In financial terms, the use of animals is only a small part of the total required to produce a licensed new medicine. Estimates of animal cost do not usually exceed five percent. See 71st Stephen Paget Memorial Lecture, available at: http://www.rds-online.org.uk/pages/news.asp?i_ToolbarID=6&i_PageID=176. Accessed on: 26 Apr 2005; AstraZeneca (2003) *Take a Walk Along the Path to a New Medicine*, available at: http://www.astrazeneca.com/sites/7/imagebank/typeArticleparam502178/seeking_new_medicines_v15.html. Accessed on: 26 Apr 2005.

6 We use the term discovery to refer to research that aims to find novel connections between diseases, molecular targets and well-characterised therapeutic interventions. We use the term development to refer to laboratory and animal studies designed to test the mechanisms, safety and efficacy of an intervention prior to its applications to humans (pre-clinical development) and to trials involving human participants to determine further the safety and efficacy of potential drug candidates (clinical development).

7 Network Science (2004) *The Process of Drug Development*, available at: http://www.netsci.org/scgi-bin/Courseware/projector.pl?Course_num=course1&Filename=top.html. Accessed on: 26 Apr 2005.

beginning with target identification and ending with the launch of the new product (see Table 8.1).[8] Data from animal research are crucially important to researchers in the pharmaceutical industry when deciding whether a potential medicine will be effective and safe for use in humans.[9]

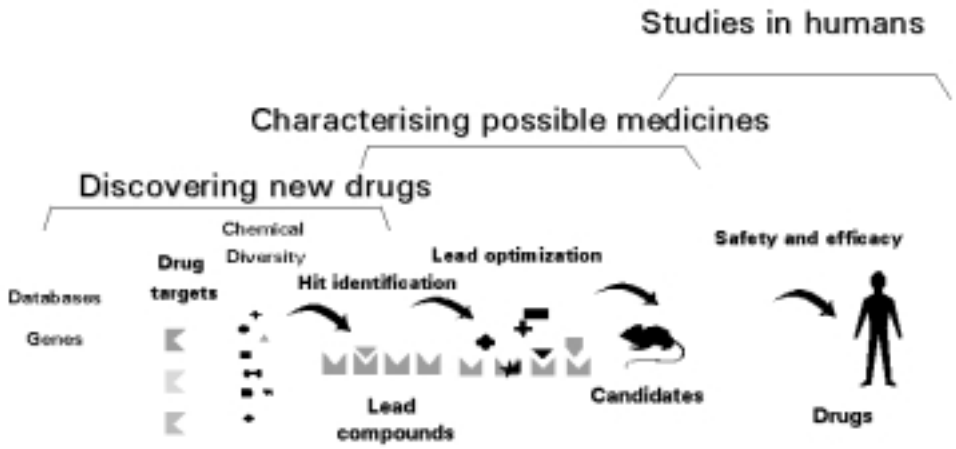


**Figure 8.2: Overview of the activities involved in modern drug discovery and development**

Source: GlaxoSmithKline

**Table 8.1: Overview of the process of discovery and development of medicines**

| Objective | Stage no. | Description | Average number of compounds entering each stage | Average use of animals |
|---|---|---|---|---|
| Discovery and selection of potential new medicines | 1 | Target identification | – | 5–15% |
| | 2 | Identification of possible medicines | 1,000,000 | |
| The characterisation of promising candidate medicines | 3 | Lead identification | 1,000 | 60–80% |
| | 4 | Lead optimisation | 200 | |
| Ensuring the safety of selected candidates | 5 | Selecting candidate medicines | 17 | 10–20% |
| Clinical studies on humans | 6 | Concept testing | 12 | Generally none |
| | 7 | Development for launch | 9 | Generally none |
| | 8 | Launch phase | 2.2 | Generally none |

8 See AstraZeneca (2003) *Take a Walk Along the Path to a New Medicine*, available at: http://www.astrazeneca.com/sites/7/imagebank/typeArticleparam502178/seeking_new_medicines_v15.html. Accessed on: 26 Apr 2005.

9 Samuels G (2003) *Medicines: Tried And Tested - In Animals?*, available at: http://www.abpi.org.uk/publications/publication_details/mttur/mttur_ani.asp. Accessed on: 26 Apr 2005.

***Stages 1 and 2: discovery and selection of compounds that could be effective medicines***

8.6 Early stages of the discovery process can be divided into two stages. Stage 1 involves target identification (seeking, for example, to identify receptors for active molecules), and stage 2 relates to the identification of possible medicines. Both stages make use of advances in genetic and basic biological research, and of new, automated technologies including:[10]

- **high-throughput chemistry**: systematic exploration of the diversity of chemical structures to increase the number of possible candidates; the aim is to produce a shortlist of novel molecules that have the potential to be safe and effective medicines;
- **ultra**[11]**-high-throughput screening**: automated analysis of a very large number of novel molecules in cell-based *in vitro* assays, which are analysed by automated systems using advanced robotics;
- **high-throughput biology**: technologies such as automated administration of medicines and automated blood collection via catheters into blood vessels, which then allow a more rapid and detailed analysis of the full range of effects in whole animals.

The very large amounts of data generated from these new methods are then integrated and analysed further by means of statistical and computational methods.

Stage 1: target identification

8.7 The search for new medicines begins by focusing on areas that are of potential interest to pharmaceutical companies. These include medicines that can be used to address unmet medical needs (for example, Alzheimer's disease), interventions against diseases that affect a great number of people, such as malaria or HIV/AIDS, medicines that are sometimes referred to as 'lifestyle drugs', such as Viagra or Propecia,[12] and improvements to existing medicines.[13] Pharmaceutical companies also sometimes seek to develop new medicines even if the medical need is already met because there appears to be access to a profitable share of the market.

8.8 Effective medicines maximise their effect on a specific biological pathway and minimise effects on all other pathways. The identification of useful *targets*, such as disease-associated genes or proteins that function as receptors for active molecules of new medicines, is therefore crucial. Information from the sequencing of the human and animal genomes is also important for the identification of disease mechanisms and for understanding how a person's genes can affect both disease processes and their responses to medicines.[14]

Stage 2: identification of possible medicines

8.9 In the next stage, compounds that might interact with the selected targets are submitted for high-throughput screening (or HTS), which is the automated testing of tens or even hundreds of thousands of compounds in a systematic way using cell based in vitro assays. Compounds or 'hits' that are judged to be the most interesting are then examined further. At the start of the process there is an average of one million compounds; at the end, numbers have decreased to about 1,000.

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10 AstraZeneca (2003) *Enabling technologies*, available at: http://www.astrazeneca.com/article/11177. GlaxoSmithKline (2003) *New Automated Approach will Transform Discovery Research at GSK*, available at: http://science.gsk.com/news/features/030613-tres.htm; GlaxoSmithKline (2003) *GSK Progresses Its Plan to Automate Discovery Research Processes*, available at: http://science.gsk.com/news/features/031021-hlw.htm. Accessed on: 26 Apr 2005.

11 The prefix 'ultra' refers to the very high throughput enabled by miniaturisation and automation.

12 Viagra was developed to treat impotence. Propecia is intended to help patients who suffer from baldness.

13 See paragraphs 3.13, 14.40, 14.58 and 15.83 for a brief discussion on similar medicines, sometimes known as 'me-too' drugs.

14 See Nuffield Council on Bioethics (2003) *Pharmacogenetics: ethical issues* (London: NCOB).

*Use of animals*

8.10 The molecules that are studied in stages 1 and 2 are screened against animals, animal tissues and cloned human receptors. The numbers of animals involved are small, probably less than ten percent of the total number used in pharmaceutical research.[15] Animal tissues are used for some *in vitro* tests, but cloned human receptors are preferred as these are more selective. GM mice are most commonly used to assess the importance of a drug target by examining the effects of deleting genes responsible for the synthesis of proteins such as receptors or other potential drug targets. The way in which the welfare of these animals is affected depends on the precise nature of the genetic modification that has been applied. Phenotypic effects may range from a lack of detectable changes to stunted growth and developmental abnormalities, and early death (paragraphs 4.57–4.58). Assessments need to be on a case by case basis as it is difficult to make generalisations.

*Vaccines*

8.11 Advances in genomic research have had a significant impact on the use of animals in the vaccine discovery process, often reducing the number involved or, leading to the replacement of animals such as primates with genetically modified mice.[16] Bacterial and viral genomes have been sequenced and potential vaccine targets are tested in high-throughput screening. The main difference in comparison to drug development is that the potential medical product under test is usually not an inorganic chemical molecule, but a biological product such as a fragment of a virus. Mapping of the human genome has also allowed the discovery of biological products that may eventually protect from, or even treat, diseases such as cancer.[17]

***Stages 3 and 4: the characterisation of promising candidate medicines***

8.12 In stages 3 and 4 the pharmacological properties of potential medicines are characterised more fully. These techniques combine use of non-animal approaches such as computer studies and analysis, chemistry and cell culture, with animal-based techniques such as advanced surgery, behavioural analysis, imaging such as MRI, and tissue and body fluid analysis (see paragraphs 4.53–4.56). New technologies such as telemetry now allow much more information to be obtained from each animal. For example, data from multiple measurements of physiological parameters such as heart rate or levels of neurotransmitters can be combined. With regard to welfare, post-operative pain can be controlled by pain relieving medicines, but sometimes they may interfere with experiments on pain and may not be given (see Box 8.3). The choice of pain relieving medicine can therefore be critical. Occasionally, distress can also be caused by devices used in telemetry (see paragraph 4.56).[18]

Stage 3: identification of 'leads'

8.13 Potential drug compounds ('hits') that have been identified by means of high-throughput screening are further examined in this stage, commonly using more complex cell cultures or assays based on animal or human tissue. The number of compounds entering this phase is usually in the hundreds. Through 'hit-to-lead chemistry', these hits are converted into a

15 The statistics collected by the Home Office do not include these data and companies vary in how they implement the various stages, making this figure difficult to estimate.

16 See The Associate Parliamentary Group for Animal Welfare (2005) *The Use of Animals in Vaccine Testing for Humans*, p21, available at: http://apgaw.org/userimages/Vaccinetesting.pdf. Accessed on: 26 Apr 2005; see also paragraph 6.35.

17 For example, see Berthet FX, Coche T and Vinals C (2001) Applied genome research in the field of human vaccines *J Biotechnol* 85: 213–26.

18 Morton DB, Hawkins P, Bevan R *et al*. (2003) Seventh report of the BVAAWF/FRAME/RSPCA/UFAW Joint Working Group on Refinement: Refinements in telemetry procedures *Lab Anim* **37**: 261–99.

significantly lower number of compounds known as 'leads'. Lead compounds are chemicals that influence the target in a way that indicates that they have high potential to be developed into effective treatments.

Stage 4: lead optimisation

8.14 Lead compounds are further refined by synthetic chemical modification, leading to the identification of a subset of the compounds that fulfil the requirements for clinical usefulness.[19] Animal and non-animal techniques are used to test for attributes such as absorption, duration of action and delivery to the target. The results determine whether the lead compounds have the potential for subsequent testing in human trials, and therefore the qualities to become candidates for medicines.

*Use of animals*

8.15 Most of the animals used by the pharmaceutical industry are involved in stages 3 and 4, comprising up to 80% percent of the total. Some techniques, such as methods for administering a medicine and measuring the level in blood, are generic for all types of research and testing (see paragraphs 4.31–4.59), but specific animal models of disease are used in particular areas of research. For example, one model may be used to identify targets for compounds to treat acute tissue damage after a stroke, whereas another may seek to find targets relevant to long-term recovery from a stroke (see Box 8.2). As we have said, an animal need not share all properties of humans to be an effective model. It is sufficient for the model to be similar in relevant aspects of the disease being studied (see paragraph 4.10).

8.16 The involvement of GM animals, usually mice, during stages 3 and 4, is becoming increasingly common. They are generally used either to determine if a gene is important as a target (target validation) or, once its importance is known, as a much more specific animal model of a disease.[20] Some tests of bioavailability (the degree or rate at which a medicine or other substance is absorbed or becomes available at the intended site in the body after administration), drug disposition and pharmacogenetic models[21] may also be used in a more limited way at this stage.

19 Physico-chemical, pharmacokinetic and toxicological properties are important criteria in assessing potential clinical usefulness.

20 Wellcome Trust (2003) *Transgenic mice*, available at: http://www.wellcome.ac.uk/en/genome/technologies/hg17b012.html Accessed on: 26 Apr 2005.

21 See MacGregor JT (2003) The future of regulatory toxicology: impact of the biotechnology revolution *Toxicol Sci* **75**: 236–48.

### Box 8.1: The characterisation of promising candidate medicines (stages 3 and 4): example of animal research undertaken during of the development process of a new medicine

Jin, Q, Nie H, McCleland BW *et al*. (2004) Discovery of potent and orally bioavailable N,N'-diarylurea antagonists for the CXCR2 chemokine receptor *Bioorg Med Chem Lett* 14:4375-8.*

The aim of this research was to test the ability of a series of compounds to bind to the CXCR2 chemokine receptor (thus blocking its function). CXCR chemokines are signalling molecules that play an important role in transporting neutrophils (a type of white blood cell) to sites of inflammation in disease processes involved in arthritis, asthma and reperfusion injury (where the body's attempt to restore blood flow to an injury causes damage by oxidation).

A non-animal *in vitro* assay was used to identify compounds which may bind to the CXCR receptor. Six compounds were identified and their affinity for the CXCR2 receptor, as well as their effect in a living body, was investigated. The degree of binding to the CXCR2 receptor was then assessed in cell lines originally derived from the kidneys of Chinese hamsters.

In a further test, the compounds were injected into groups of three rats. This was first done intravenously and then, in a later experiment, injected into the peritoneal cavity. This experimental format is designed to both reduce the number of animals used and experimental variation. At various intervals after administration of the compounds, blood samples were taken from the lateral tail vein of the rats. Further *in vitro* studies using components of rat and human liver cells were carried out to investigate the way that the liver metabolises these compounds. These cells were obtained from euthanised rats and from human tissue which had been removed during surgery. The research yielded a new class of CXCR2 compounds that are potent and effective in binding and blocking CXCR2 receptor function.

* This is an example of animal research that has been carried out in the UK and published in a peer-reviewed journal. Details relate to this specific example and should not be taken to represent a 'typical' animal experiment. It is important to note that individually published experiments usually form one part of a continuing area of research, and the significance of the results may therefore be difficult to interpret.

### Box 8.2: The characterisation of promising candidate medicines (stages 3 and 4): example of animal research undertaken during the development process of a new medicine

Irving EA, Vinson M, Rosin C *et al*. (2005) Identification of neuroprotective properties of anti-MAG antibody: a novel approach for the treatment of stroke? *J Cereb Blood Flow Metab* **25**: 98–107.*

It had been previously hypothesised that a protein called myelin-associated glycoprotein (MAG) was a contributing factor to the lack of regeneration of the CNS after injury, such as stroke. This research project demonstrated that the antibody specific to this protein, anti-MAG, possessed the ability to neutralise the inhibitory effect of MAG on neurons following an induced stroke and, in addition, protected certain CNS cells from cell death *in vitro*. Rats given the antibody improved in their motor function ability after the stroke compared with control animals, measured by their ability to walk along a cylindrical beam. The authors concluded that the data indicated potential for the use of the antibody as a therapeutic agent for the treatment of stroke.

Under anaesthesia, small tubes were inserted into the brains of rats to enable the induction of a stroke. Two weeks later the rats were anaesthetised and a stroke was induced by causing a transient blockage of an artery in the brain for 90 minutes. Rats that displayed circling stereotypic behaviour one hour following the surgical procedure were judged to be suitable models and therefore only these rats were included in the study. During the following week, the rats were administered with the test antibody at 1, 24 and 72 hours after the stroke either into the brain or intravenously. They were then euthanised.

* This is an example of animal research that has been carried out in the UK and published in a peer-reviewed journal. Details relate to this specific example and should not be taken to represent a 'typical' animal experiment. It is important to note that individually published experiments usually form one part of a continuing area of research, and the significance of the results may therefore be difficult to interpret.

8.17 Information about research carried out during stages 3 and 4 is often provided through oral communications and posters at scientific meetings, and is later reported in scientific publications.[22] Many thousands of such posters and publications are published annually by industry. More recently, the Home Office has begun to make available abstracts of licensed research (see Box 13.4), which are likely to include many types of experiment undertaken to identify and optimise pharmaceutical leads. We consider issues relating to publication of research in more detail in Chapter 15 (see paragraph 15.35).

22 See PubMed, a service of the US National Library of Medicine, which includes over 15 million citations for biomedical articles dating back to the 1950s, available at: http://www.ncbi.nlm.nih.gov/pubmed. Accessed on: 26 Apr 2005.

*Vaccines and veterinary medicines*

8.18 Characterisation of vaccines and other biological products during stages 3 and 4 has a number of special features. First, the product may require modification so that it can be administered and remain effective as it is absorbed and transported around the body. Secondly, vaccines commonly contain an adjuvant (e.g. aluminium hydroxide) which is used to increase the effectiveness of the immune response. Both vaccine modification and testing of adjuvants involve the use of animals. The product is often administered to animals and their immune responses are measured by sampling blood and tissue.[23] For example, vaccines against tetanus are tested for potency in mice or guinea pigs. Animals are given the tetanus vaccine (which should confer protection) and later receive what would be expected to be a lethal or paralytic dose of tetanus toxin. If the vaccine has the required potency, the toxin will cause no adverse effects for the animals (see also Box 8.5).[24] In the past, many more tests were required during which the animals showed symptoms of the disease, which could be severe and even lead to death. This methodology has been replaced in many cases by earlier, more humane, experimental endpoints (see paragraph 5.22), such as changes in weight, body temperature or behaviour.[25] In addition, blood and tissue markers of infection are increasingly used.[26]

8.19 The development of new veterinary medicines often involves studies that use the same species for which the medicine is intended. Usually, animals with specific diseases are used as models, although animals spontaneously affected by the disease or condition are also used in field studies.[27] The effect on the animals is specific to the area of research, and may depend also on the state of their health. For example, in the case of the severe respiratory disease pasteurellosis, which affects cattle, 450 calves were used in a programme to develop a vaccine and a significant proportion suffered from the disease.[28] The vaccine that was developed has now been used successfully to bring the disease under control.[29] In field trials potential suffering is usually avoided by comparing the new vaccine to existing treatments (if available) rather than using placebos as a comparison.

***Stage 5: selecting candidate medicines and ensuring their safety***

8.20 The aim of stage 5 is to decide whether promising compounds could be tested in trials involving human volunteers. Questions that need to be addressed include:

- Do particular compounds meet the quality threshold to be a successful medicine?
- Would the medicine be safe and effective for humans?
- How best could the medicine be administered?

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23 Leenaars PPAM, Hendriksen CFM, de Leeuw WA *et al*. (1999) The production of polyclonal antibodies in laboratory animals ECVAM Workshop Report 35 *ATLA* **27**: 79–102.

24 See Weisser K and Hechler U (1997) *Animal Welfare Aspects in the Quality Control of Immunobiologicals: A critical evaluation of animal tests in pharmacopoeial monographs* (Nottingham: FRAME, ECVAM and the Paul Ehrlich Institut).

25 See Hendriksen CFM and Morton DB (Editors) (1999) *Humane Endpoints in Animal Experiments for Biomedical Research* Proceedings of the International Conference, 22–25 Nov 1998, Zeist, The Netherlands (London: Royal Society of Medicine), available at: http://www.lal.org.uk/endpoints1.html. Accessed on: 26 Apr 2005.

26 Griffin JF (2002) A strategic approach to vaccine development: animal models, monitoring vaccine efficacy, formulation and delivery *Adv Drug Deliv Rev* **54**: 851–61.

27 This is regulated under the authority of Animal Test Certificates (ATC). See Veterinary Medicines Directorate (2004) *Animal Test Certificates*, available at: http://www.vmd.gov.uk/lu/amelia/amelia13n.pdf. Accessed on: 26 Apr 2005.

28 This would have included the animals used as the positive controls (to prove the bacteria could cause the disease) and unprotected animals that had been administered trial vaccines that proved ineffective.

29 National Office of Animal Health (2002) *Vaccination of farm animals*, available at: http://www.noah.co.uk/issues/briefingdoc/22-vaccfarmanimals.htm. Accessed on: 3 May 2005.

- How much of the medicine will be active in the body?
- Is it possible to produce enough of the active compound at an acceptable cost?

8.21 Once a candidate drug has been selected, toxicity studies are then conducted on animals, completing the pre-clinical phase of the development process.[30] The increased knowledge gained in the earlier stages of the modern drug-discovery process means that potential medicines are now better characterised by the time that the toxicity studies begin. Extrapolations are made from animal and non-animal data to predict safety and the initial dose of medicines to be used in humans. The use of toxicity databases, toxicogenomics, proteomics and high-throughput screening (see paragraph 8.6) play an important role in providing additional information and helping to reduce the use of traditional toxicity studies. Together with data from non-animal studies, pre-clinical results of these tests are submitted to regulatory authorities in the application for permission to conduct clinical studies in human volunteers. The final outcome of this stage is a candidate drug that meets the safety criteria set by regulatory bodies and has the potential to be developed into a successful and commercially viable product.

*Use of animals*

8.22 At this, and subsequent stages, toxicity tests on animals are undertaken to meet the requirements of regulators that a potential medicine demonstrates an acceptable balance of safety and efficacy (see paragraphs 9.6–9.21). The custom and practice of regulatory agencies has been to rely on data from animal research when making these judgements, although increasingly more data from validated non-animal methods are generated and accepted. Toxicity studies account for between five and 20 percent of animal use by the pharmaceutical industries. In 2003, pharmacological safety and efficacy evaluation constituted ten percent of the total number of animal procedures in Great Britain.[31] Animal tests at this stage are much more uniform compared to the experiments carried out in drug discovery and they need to be conducted in a format that is accepted worldwide. Some of the most important tests, and associated welfare implications, are described in Chapter 9, in which we discuss toxicity testing in more detail. (The scope of Refinements,[32] and the application of the Three Rs in toxicity testing more generally, are considered in Chapters 11 and 12).

*Vaccines and veterinary medicines*

8.23 Before administering a novel vaccine to human volunteers researchers need to ensure that the candidate vaccines will not infect trial participants with the disease (as might be possible with live vaccines) or lead to an inappropriate immune response, such as producing antibodies that have adverse effects. It also needs to be ascertained whether the agent, or additives such as adjuvants, are likely to cause direct irritation at the site of application. The

30 The pre-clinical phases (discovery, selection and characterisation of promising candidate medicines and toxicity studies) take on average four to five years to perform, and cost on average £200 million. See Network Science (2004) *The Process of Drug Development*, available at: http://www.netsci.org/scgi-bin/Courseware/projector.pl?Course_num=course1&Filename=top.html. Accessed on: 26 Apr 2005.

31 Eighty-three percent of toxicological procedures were performed to comply with legislative or regulatory requirements. See Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (London: HMSO).

32 Refinements can be implemented through the use of more sensitive markers of toxicity (for example, blood tests or remote monitoring) and more humane endpoints. See Organisation for Economic Co-operation and Development (2000) *Guidance Document on the Recognition, Assessment, and Use of Clinical Signs as Humane Endpoints for Experimental Animals Used in Safety Evaluation*, available at: http://www.olis.oecd.org/olis/2000doc.nsf/4f7adc214b91a685c12569fa005d0ee7/c125692700623b74c12569bb005aa3d5/$FILE/00087372.PDF. Accessed on: 26 Apr 2005.

common types of test required are single- and repeated-dose toxicity assessments and testing to determine any local irritation (see paragraphs 9–9-9.18).[33] Specific tests are also required to determine how effective the vaccine is in protecting animals against challenge with the pathogen. In order to assess efficacy, the test vaccine is administered to animals and the disease is subsequently induced. If the vaccine does not protect the animals they may experience pain or suffering related to the disease, although humane endpoints are usually chosen. Animals are euthanised when these are reached.

8.24 Veterinary medicines are generally evaluated for safety using the species in which they will eventually be used (see paragraph 8.19).

***Stages 6–8: clinical studies on humans***

8.25 Potential new medicines are first tested on small groups of healthy human volunteers, and then on progressively larger groups of patients.[34] These tests are organised into four consecutive trials, Phases I–IV (see Figure 8.3). Experimental medicine has enlarged the application of existing clinical tests that are used in these studies. They include advanced blood and tissue diagnostics, and imaging techniques, such as MRI or PET scanning (see paragraph 5.12 and Box 11.1).

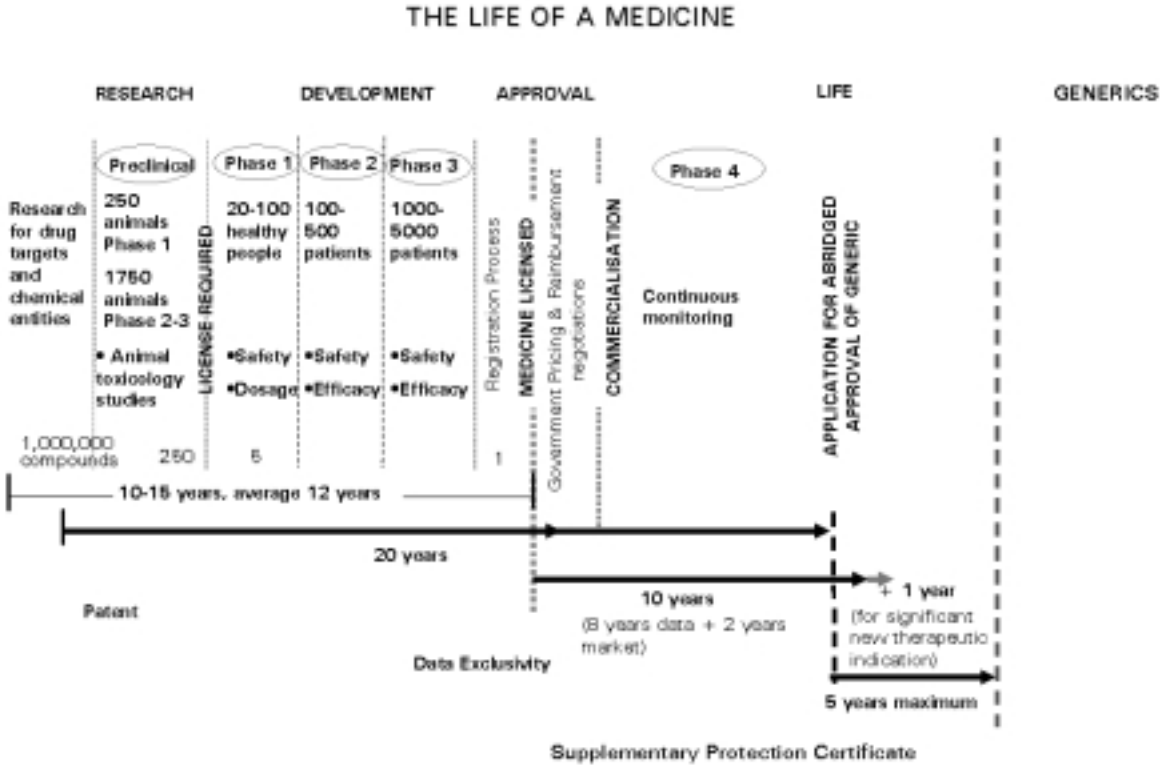


**Figure 8.3: The path to modern medicine – phases of pre-clinical and clinical development**

Source: GlaxoSmithKline

33 The European Agency for the Evaluation of Medicinal Products (1997) *Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines*, available at: http://www.emea.eu.int/pdfs/human/swp/046595en.pdf. Accessed on: 26 Apr 2005.

34 See ABPI (2003) *Clinical Trials - Developing New Medicines*, available at: http://www.abpi.org.uk/publications/briefings/clinical_brief.pdf. Accessed on: 26 Apr 2005.

Stage 6: concept testing

8.26 Typically, no more than a few candidate medicines for any given disease enter this stage. In Phase I of clinical trials, they are first tested in a limited number of healthy volunteers (see Figure 8.3). The purpose is to determine how well the active ingredient is actually tolerated in humans and whether it has the desired effect, to obtain information about suitable dosage and to determine whether it has characteristics that would allow it to be developed into a medicine.

*Use of animals*

8.27 During the subsequent Phases II–IV, additional animal studies that aim to ensure the safety of the particular medicine and its application are undertaken. For example, if a medicine is intended to be given to women of childbearing age, reproductive toxicology would be assessed in animals prior to Phase II studies (see paragraphs 9.22–9.23 and Box 8.4).

Stage 7: development for launch

8.28 If testing in healthy volunteers (Phase I) and a limited number of patients (Phase II) is successful then large-scale trials involving human volunteers are carried out (Phase III). Phase III trials involve between 1,000 and 5,000 patients, and provide the basis for the final decision as to whether to continue or abandon the project. The size and scale of Phase II and III studies make this stage the most expensive part of drug development (see Figure 8.3).[35]

*Use of animals*

8.29 During clinical studies on humans, Phases I–III, a comprehensive set of safety tests in animals continues to be carried out. The project team that is developing the medicine liaises with the internal ethics committee and regulatory authorities, to define the tests that are required to ensure safety (see paragraphs 9.4–9.25).

*Vaccines and veterinary medicines*

8.30 The clinical development of vaccines may require further safety tests in animals, which are broadly similar to those required for human medicines.[36] The exact nature of these tests depends on the results of clinical trials.[37] The data required for a marketing authorisation for a veterinary medicine concern proof of efficacy and bioavailability of a product.[38] The scale and scope of the data provided are generally less comprehensive than for human medicines, although in some cases specific emphasis is given to certain areas. For example, in the case of food-producing animals, evidence is required on the potential for residues of new medicines to accumulate in food.[39] Bioavailability studies are similar to those undertaken for human medicines (see paragraph 9.24), although more-invasive muscle tissue samples may be taken in order to test for residues.

35 The average length of clinical phases (concept testing and development for launch) is eight to twelve years and the average cost of clinical phases is £350 million, see The Association of the British Pharmaceutical Industry *The Development of Medicines*, available at: http://www.abpi.org.uk//publications/briefings/Dev_Medicines.pdf. Accessed on: 26 Apr 2005.

36 The tests described in Chapter 9 may also apply to vaccines.

37 The European Agency for the Evaluation of Medicinal Products (1997) *Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines*, available at: http://www.emea.eu.int/pdfs/human/swp/046595en.pdf. Accessed on: 26 Apr 2005.

38 Veterinary Medicines Directorate (2002) *Application Form for a Marketing Authorisation*, available at: http://www.vmd.gov.uk/lu/forms/appform1a.pdf. Accessed on: 2 May 2005.

39 See Veterinary Residues Committee *Fact Sheet*, available at: http://www.vet-residues-committee.gov.uk. Accessed on: 2 May 2005.

Stage 8: launch phase

8.31 At this stage, the data from all of the pre-clinical and clinical studies are collated and sent to the regulatory agencies (see paragraphs 9.4 and 13.49–51). The average time for regulatory approval is 1.5 years.

*Use of animals*

8.32 There is usually no animal use at this stage.

***Support for the marketed medicine***

8.33 Once a medicine is approved by the regulatory agencies, Phase IV clinical trials monitor long-term effects in large numbers of patients and evaluate economic aspects of the medicine. Extensive programmes to capture information on disease epidemiology and the outcomes of using the medicine may be established. This information gathering may also include sampling, for example to obtain pharmacogenetic data, to inform the very first stages of drug discovery. New indications and new formulations are also closely examined. Medicines originally intended for treatment of one disease are sometimes found to have beneficial effects for others (see Boxes 8.3 and 8.4).

### Box 8.3: Testing approved drugs for a novel use: example of animal research undertaken after a medicine is on the market

Fox A, Gentry C, Patel S, Kesingland A and Bevan S (2003) Comparative activity of the anti-convulsants oxcarbazepine, carbamazepine, lamotrigine and gabapentin in a model of neuropathic pain in the rat and guinea pig *Pain* **105**: 355–62.*

The aim of this research was to find out whether drugs that are currently used to treat epilepsy could also be effective as pain killers for persistent neuropathic pain. This form of pain is produced by the nervous system itself, 'phantom' limb pain in amputees being one extreme example. Clinical management of neuropathic pain is very difficult as it responds poorly to opiates and non-steroidal anti-inflammatory medicines. It is treated primarily with anti-epileptic medicines and anti-depressants, although both are associated with significant use-limiting adverse effects. The researchers concluded from their experiments on guinea pigs and rats that some of the anti-epileptic medicines administered were able to relieve neuropathic pain, although the effects differed between the two species. These new medicines were not accompanied by the use-limiting side effects exhibited by current treatments for neuropathic conditions.

In some animal models for neuropathic pain, the spinal or facial nerves of the animal have been fused, leading to the development of a long-lasting pain response. In this example, guinea pigs and rats had the sciatic nerve in one leg surgically exposed, and one third to one half of its thickness was tied with a suture under anaesthetic. The aim of this intervention was to reproduce the exacerbated response that sufferers from neuropathic pain experience in response to a normally mild stimulus. The animals were allowed to recover for approximately two weeks after surgery. Post-operative painkillers were not used since the development of pain was the object of the study. Following recovery, the researchers assessed the pain response by applying increasing pressure to the paws of the animals. The threshold at which the animal flinched was measured for both the injured and the uninjured hind paw after which greater pressure was not applied. The medicine under test was then administered and the same procedure was carried out for up to six hours thereafter, and repeated for up to six days.

A further experiment was carried out on rats to measure the pain response to a stimulus that would not usually cause pain. Thin filaments were applied to both hind paws, starting with a low force. This was repeated five times at intervals of one or two seconds and the response noted. The researchers waited for at least five minutes between using successively stiffer filaments. The filament force that produced a withdrawal of the paw was denoted as the threshold for the stimulus, after which greater pressure was not applied. Thresholds were determined prior to and up to six hours following drug administration. All animals showed an increased sensitivity to pain following the surgical procedure.

* This is an example of animal research that has been carried out in the UK and published in a peer-reviewed journal. Details relate to this specific example and should not be taken to represent a 'typical' animal experiment. It is important to note that individually published experiments usually form one part of a continuing area of research, and the significance of the results may therefore be difficult to interpret.

### Box 8.4: Use of thalidomide

Thalidomide is a notorious example of the failure of methodology in pharmaceutical research.* The example is frequently used to argue that the results of animal studies cannot be applied to humans. Thalidomide was licensed as a sedative after safety tests performed on animals were approved by the regulatory authorities. Between 1957 and 1961 it was prescribed to pregnant women as a treatment for morning sickness and other symptoms. In December 1961 *The Lancet* published a letter by Dr W.G. McBride, an Australian obstetrician, stating that he had observed frequent limb deformities in babies of women who had taken thalidomide during pregnancy. It later emerged that more than 10,000 children around the world had been affected.†

Research published five months after Dr McBride's letter confirmed that thalidomide given to pregnant rabbits resulted in the birth of litters with similar limb deformities to those in humans. Subsequent research showed that offspring of mice, rats, hamsters, macaques, marmosets, baboons and rhesus monkeys suffered comparable effects. Although the licensing of thalidomide involved animal research, tests on pregnant animals were not undertaken as this was not a legal requirement. Partly in response to the thalidomide tragedy, the UK passed the Medicines Act of 1968, which regulates the testing and supply of medicines in the UK (see paragraph 13.49).‡

Strict measures have been put in place in many countries to prevent the use of thalidomide by pregnant women. At the same time, the drug has been found to be an effective treatment for other conditions. Celgene Corporation has begun developing the medicine for a range of potential indications, including AIDS-related, dermatological and cancer-related conditions.∫

In 1998 the US Food and Drug Administration granted marketing clearance to Celgene's Thalomid for the treatment of erythema nodosum leprosum (ENL), a severe and debilitating condition associated with leprosy (Hansen's disease). The Authority also imposed unprecedented restrictions on the distribution of the medicine. These included restriction on those who were permitted to prescribe thalidomide, a requirement for a negative pregnancy test result within 24 hours of starting therapy and weekly testing during the first month of use. Women were also required to use two reliable forms of contraception simultaneously while taking the drug.**

* See RDS Thalidomide, available at: http://www.rds-online.org.uk/pages/page.asp?i_ToolbarID=5&i_PageID=1070 . Accessed on: 2 May 2005.

† Powell RJ (1996) New roles for thalidomide *BMJ* **313:** 377–8.

‡ ABPI Law - Approval of medicines, available at: http://www.abpi.org.uk/amric/basic5.asp. Accessed on: 2 May 2005.

∫ See Celgene Thalomid, available at: http://www.celgene.com/Products.aspx?s=1. Accessed on: 21 April 2005; see also Pollard M (1996) Thalidomide promotes metastasis of prostate adenocarcinoma cells (palii) in L-W rats. Cancer Lett 101: 21-4

** Food and Drug Administration (1998) FDA approves thalidomide for Hansen's disease side effect, imposes unprecedented restrictions on distribution, available at: http://www.fda.gov/bbs/topics/answers/ans00887.html. Accessed on: 2 May 2005.

*Use of animals*

8.34 Limited animal use may be required for new indications, new formulations or in studies of possible adverse effects in patients. However, there is much reliance on archived animal and human testing data.

*Vaccines*

8.35 An exception to limited use of animals at this stage occurs in vaccine testing. Immunisation is a very cost-effective public health intervention and billions of doses of vaccine are administered each year for the prevention of a range of diseases.[40] Relatively large numbers of animals are used for toxicity testing of batches of these vaccines. This is because the exact composition and properties of many biological products are very difficult to control and may alter after production.[41] Continuous safety and efficacy testing of production batches of vaccines is therefore carried out.[42]

8.36 Depending on the type of test, there may be serious welfare implications. For example, if death is the required endpoint, or if it is the most convenient stage for reliable

40 See World Health Organization (2003) *Vaccines, Immunization and Biologicals – Statistics and Graphics*, available at: http://www.who.int/vaccines-surveillance/StatsAndGraphs.htm. Accessed on: 26 Apr 2005.

41 For example, the reactivation by mutation of inactivated viruses needs to be monitored and assessed.

42 The recent report by the Associate Parliamentary Group for Animal Welfare on vaccine testing describes why such quality control is required, the animals that are used, the pain and distress that they experience and the current use, and prospects for, Replacement, Reduction and Refinement. See The Associate Parliamentary Group for Animal Welfare (2005) *The Use of Animals in Vaccine Testing for Humans*, available at: http://apgaw.org/userimages/Vaccinetesting.pdf. Accessed on: 26 Apr 2005.

observation, then it may be used, subject to regulatory approval. While the terminal stages of a lethal endpoint may not involve much, if any, suffering as the animal may be comatose, the suffering that may have taken place beforehand can be substantial and may have involved symptoms such as inappetence (lack of appetite), malaise, convulsions or paralysis (see also Box 8.5).

### Box 8.5: Examples of animal suffering in the context of quality control of vaccines for human use*

***Tetanus potency test***

Batches of tetanus vaccine are tested for potency in mice or guinea pigs. The standard method involves testing a new vaccine against a reference vaccine at three different concentrations. It has been estimated that 66–108 animals are usually used for each test. The animals are administered with the vaccine under the skin and four weeks later with a single dose of tetanus toxin. This dose could be lethal or paralytic. Control animals (that receive no vaccine) and those animals that are unprotected because the test vaccine they receive is unsuitable or is at an ineffective concentration suffer paralysis and death.

***Diptheria (absorbed) potency test***

Guinea pigs are immunised with test samples of diphtheria vaccine, and are subsequently infected with diphtheria bacteria four weeks later. In the EU, both lethal and non-lethal amounts of the bacterial toxin are permitted for this test and the endpoints are death or skin inflammation respectively. At least three dilutions each of the test vaccine and a reference vaccine are used, together with one untreated control group. A minimum of 70 animals is used to test each vaccine batch and both methods cause severe pain and distress for those animals that are unprotected (see above). There is no agreement on whether the lethal or non-lethal methods cause greater suffering.

* See The Associate Parliamentary Group for Animal Welfare (2005) The Use of Animals in Vaccine Testing for Humans, available at: http://apgaw.org/userimages/Vaccinetesting.pdf Accessed on: 26 Apr 2005.

## The validity of animal models used in pharmaceutical research

8.37 We have described why and how animals are used in pharmaceutical research and have illustrated with several examples the range of welfare implications that they may experience. Many people who are concerned about animal suffering are critical of the permissibility of animal research on ethical grounds. However, there are critics who also object to the use of animals in pharmaceutical research on scientific grounds. They question the transferability and predictability of data obtained from animals, and its reliability for the accurate assessment of the safety of new therapeutic interventions, as shown by the following respondents to the Consultation:

> '…animal experimentation is positively harmful to human health… [It] does not provide information that is relevant to human medicine because the data cannot be transferred to humans with any degree of reliability. In fact, studies of the predictability of animal experiments consistently show them to be worse than random guesswork… Adverse drug reactions are the fourth leading cause of death in the Western world, killing over 100,000 individuals every year in the US alone. Clearly, the animal tests are failing to protect people.'
> *Animal Aid*

> '…claims that animal experiments have instilled a misplaced sense of the relative danger of a drug are supported by the incidences of false negatives and false positives known to be attached to such tests.'
> *Cris Iles-Wright*

8.38 We have shown above that producing a new medicine is a lengthy and complex process, and that decisions on the compounds that should proceed to the next stage are taken using a wide range of information. Tests on animals play a vital role, but they are not the only source of information that is used to determine safety and efficacy (see Figure 8.3). Some critics of animal research and testing tend to attribute any problems with the final product solely to the use of animal testing. We consider the general question of whether or not

animals are useful models for humans in medical research in paragraphs 10.27–10.32). Systematic limitations faced by any modelling approach are addressed in paragraphs 10.33–10.36), and the findings of scientific reviews on the critical evaluation of research involving animals are discussed in paragraphs 10.37-10.43).

8.39 We observe that claims that animal research is failing to protect people from adverse drug reactions (ADRs) need to be treated with some caution. ADRs[43] have a number of causes. Many of these are avoidable, for example where they arise from prescription errors, where people have been given or have taken the wrong medicine, or from interactions between different medicines taken simultaneously. In 2004, researchers conducting the largest prospective analysis in the UK of ADRs as a cause of admission to hospital found that more than 70% were avoidable and could have been predicted by taking into account pharmacological properties of the medicines involved.[44] While ADRs may be the direct result of administration of one specific medicine, the question remains whether this is proof of the failure of the animal model (or any other model) involved in the development process, or a methodological problem. As we have said, phases I–II of human clinical trials in the development of a medicine include up to 5,000 patients to monitor efficacy and safety. If severe ADRs occur during these trials, the development of the medicine is not usually taken further. However, ADRs may occur at very low statistical frequencies, for example 1 in 10,000, and hence may not be revealed at this stage (see paragraphs 10.33 and 10.1). In making inferences about the occurrence of ADRs, and the role that animal research plays, it is therefore unhelpful to generalise. ADRs can occur for a number of reasons and could, in principle, also be caused by a medicine that, hypothetically, had been developed without the use of animals.

8.40 Some also argue that the withdrawal of medicines from the market is indicative of the fact that animal research does not help to prevent ineffective or harmful medicines being used by humans.[45] In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) monitors whether medicines on the market meet the appropriate standards of safety, quality and effectiveness. When there is sufficient evidence to suggest that the risk of taking a medicine outweighs its benefit to patients, the Committee on Safety of Medicines (CSM) and MHRA take appropriate regulatory action to protect the health of patients, and may initiate steps to withdraw medicines from use. Between 1995 and 2005, 18 medicines were withdrawn from the UK market by companies or by the Licensing Authority on grounds of safety (see Box 8.6). A study conducted in 1994 on medicines withdrawn between 1961 and 1992 concluded that in the UK, 49 were taken off the

43 Edwards and Aronson define an ADR as 'an appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.' See Edwards IR and Aronson JK (2000) Adverse drug reactions: definitions, diagnosis, and management *Lancet* **356**: 1255–9.

44 The researchers, using Edwards and Aronson's definition of ADRs (see previous footnote), sought to ascertain the burden of ADRs though a prospective analysis of hospital admissions to two large general hospitals in the UK. Every patient aged over 16 years who was admitted to these hospitals (18,820 patients) over a six month period was assessed to determine if the admission had been caused by an ADR. It was found that 1,225 admissions were related to ADRs (equalling 6.5%, which is consistent with an estimate of 5% based on pooled data from several studies worldwide). Three types of avoidability were assessed: definitely avoidable (7-10%: the ADR was due to treatment inconsistent with present day knowledge of good medical practice), possibly avoidable (60-66%: the ADR could have been avoided by an effort exceeding the obligatory demands of present day knowledge of good medical practice) and unavoidable (25-30%: the could not have been avoided by any reasonable means). See Pirmohamed M, James S, Meakin S *et al*. (2004) Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients **BMJl 329:** 15–9. See also Waller P and Rawlins **P A User's Guide to the Safety of Medicines,** available at: http://www.dsru.org/pat_guide_1.html. Accessed on: 2 May 2005; Kohn LT, Corrigan JM and Donaldson MS (Editors) (2000) *To Err is Human: Building A Safer Health System*, available at: http://www.iom.edu/report.asp?id=5575. Accessed on: 26 Apr 2005.

45 See BUAV Don't we need animal experiments to make sure drugs are safe for humans?, in *Frequently asked questions about vivisection*, available at: http://www.buav.org/faqs.html. Accessed on: 2 May 2005.

market (see Box 8.7). These withdrawals were mainly due to inadequate evidence of efficacy in widespread clinical use, loss of therapeutic interest or poor market performance. To what extent the withdrawal of medicines can be attributed exclusively, or in part, to the use of animals in research would need to be assessed in individual cases (see paragraphs 10.27–10.43).[46]

### Box 8.6: Medicines withdrawn in the UK for safety reasons 1995–2005

| Name of medicine (brand name ) | Year action taken | Primary safety concerns |
|---|---|---|
| Naftidrofuryl oxalate injection (Praxilene) | 1995 | Cardiotoxicity |
| Pemoline (Volital) | 1997 | Liver toxicity |
| Troglitazone (Romazin) | 1997 | Liver toxicity |
| Fenfluramine (Ponderax) | 1997 | Heart valve disease |
| Dexfenfluramine (Adifax) | 1997 | Heart valve disease |
| Sertindole (Serdolect)* | 1998 | Disorders of heart rhythm |
| Tolcapone (Tasmar)† | 1998 | Liver toxicity |
| Mibefradil (Posicor) | 1998 | Drug interactions |
| Trovafloxacin (Trovan)‡ | 1999 | Liver toxicity |
| Grepafloxacin (Raxar) | 1999 | Disorders of heart rhythm |
| Pulmonary surfactant (Alec) | 2000 | Increased mortality |
| Cisapride (Prepulsid) | 2000 | Disorders of heart rhythm |
| Droperidol (Droleptan) | 2001 | Disorders of heart rhythm |
| Cerivastatin (Lipobay) | 2001 | Muscle toxicity |
| Levacetylmethadol (Orlaam) | 2001 | Cardiac arrhythmias |
| Kava kava | 2003 | Liver toxicity |
| Rofecoxib (Vioxx) | 2004 | Myocardial infarction/stroke |
| Valdecoxib (Bextra) | 2005 | Serious skin reactions |

* Sertindole has since been reintroduced under very restricted conditions.

‡ Tasmar, Trovan and Orlaam were licensed through the centralised procedure with the European Commission as the Licensing Authority.

‡ Trovafloxacin was never marketed in the UK.

Source: MHRA

46 See also Chapter 6, footnote 40.

## Box 8.7: Medicines withdrawn from the market*

Between 1961 and 1992 a total of 131 medicines were withdrawn from France (63), Germany (58), UK (49) and USA (41) (note that some were withdrawn from more than one country). Only ten were withdrawn in all four countries. In the UK the 49 withdrawn medicines can be separated into four groups, as follows:

**1) Medicines withdrawn after long-term use, which were marketed before detailed animal or clinical tests, or in use despite known toxicity, and later replaced by a medicine for the same indication with less toxicity**

| Product | Year of launch | Year withdrawn |
|---|---|---|
| Aspirin (paediatric form) | 1899 | 1986 |
| Aminopyrine | 1900 | 1975 |
| Clioquinol | 1930 (1900) | 1981 |
| Dipyrone | 1930 | 1977 |
| Oxyphenisatine | 1955 | 1978 |
| Oxyphenbutazone | 1962 | 1984 |
| Phenacetin | 1900 | 1980 |
| Phenformin | 1959 | 1982 |

**2) Medicines withdrawn because of toxicity (generally carcinogenicity) revealed by animal tests that were continued after launch**

| Product | Year withdrawn |
|---|---|
| Alclofenac | 1979 |
| Chlormadinone | 1970 |
| Danthron | 1987 |
| Fenclofenac | 1984 |
| Indoprofen | 1983 |
| Megestrol | 1970 |
| Methapyrilene | 1979 |
| Polidexide | 1975 |

**3) Medicines withdrawn for reasons unrelated to standard investigation of toxicity (i.e. particular type of toxic effect apparent after launch)**

| Product | Reason for withdrawal |
|---|---|
| Alphaxalone | Allergy to excipient |
| Cromoglycate (eyedrops) | New formulation (untested) |
| Desensitising vaccines | Allergy |
| Doxylamine | Alleged teratogenicity |
| Factor VIII | Risk of AIDS transmission |
| Growth hormone (natural) | Possibility of CJD transmission |
| Guanethidine (eyedrops) | New formulation (untested) |
| Indomethacin-R | New formulation (untested) |
| Mebanazine | Toxic interaction with diet or other drugs |
| Nialamide | Toxic interaction with diet or other drugs |
| Phenoxypropazine | Toxic interaction with diet or other drugs |
| Thalidomide | Teratogenicity not tested for |
| Zomepirac | Allergy |

*Continued*

**4) Medicines withdrawn due to unexpected toxicity**

| Product | Year of withdrawal | Reason |
|---|---|---|
| Benoxaprofen | 1982 | Toxicity in the aged |
| Benziodarone | 1964 | Hepatotoxicity |
| Domperidone injection | 1986 | Cardiovascular effects |
| Feprazone | 1984 | Multiple |
| Ibufenac | 1968 | Hepatotoxicity |
| Methandrostenolone | 1982 | Endocrine effects |
| Metipranolol | 1990 | Ophthalmological |
| Mumps vaccine | 1992 | Neuropsychiatric |
| Nomifensine | 1986 | Haematological |
| Practolol | 1975 | Rare idiosyncrasy |
| Prenylamine | 1989 | Cardiovascular |
| Propanidid | 1983 | Allergic type |
| Sulphamethoxypyridazine | 1986 | Haematological |
| Suprofen | 1987 | Nephrotoxicity |
| Temafloxacin | 1992 | Multiple |
| Terodiline | 1991 | Cardiovascular |
| Thenalidine | 1961 | Haematological |
| Triazolam | 1991 | Neuropsychiatric |
| Tryptophan | 1990 | Multiple |
| Zimeldine | 1983 | Neuropsychiatric |

* Spriet-Pourra C and Auriche M (1994) *Drug Withdrawal From Sale*, 2nd Edition (Richmond: PJB Publications).

8.41 Lastly, animal research is also undertaken by the pharmaceutical industry to refine the predictive capacity of data obtained from animal and human studies. For example, researchers seek to identify how results from different species can be best integrated in order to develop better predictions of how the medicine will be distributed, absorbed and excreted in the human body (see Boxes 8.8 and 9.4).

### Box 8.8: Example of animal research undertaken to improve the predictability of pharmacokinetic data

Aviles P, Pateman A, San Roman R *et al*. (2001) Animal pharmacokinetics and interspecies scaling of sordarin derivatives following intravenous administration *Anitmicrob Agents Chemother* **45**: 2787–92.*

The aim of this research was to compare the pharmacokinetics of a group of synthetic antifungal agents against reference compounds in different animal species and to assess whether human pharmacokinetics could be reliably predicted from this information.

The antifungal agents that were used belong to a new group of synthetic chemicals called sordarin derivatives which have been shown to prevent the growth of fungal pathogens. Opportunistic fungal pathogens remain a common cause of death in immunocompromised patients, such as those with HIV/AIDS or those receiving chemotherapy or immunosuppressive therapy.

The study used *Cynomolgus* monkeys, rats, mice and rabbits. Gunn rats, which have impaired liver function, were used to assess the processing of sordarin derivatives when they pass through the liver. A representative sordarin derivative was administered intravenously to animals. In mice, this was achieved by puncture of the tail vein. The compound was administered through tubes inserted into the jugular veins of rats and into marginal ear veins of rabbits. In monkeys, administration was performed via the cephalic vein. Each compound was administered once. In mice, blood samples were taken by cardiac puncture using a needle at eight intervals after administration. Three mice were euthanised by cervical dislocation at each sampling point. Samples of rat blood were taken from the end of the tail. Rabbits were sampled using a tube placed in the central artery of the ear. Samples of monkey blood were obtained from the posterior of the animals by direct venepuncture using a needle at ten intervals after administration.

Blood samples were allowed to clot and then centrifuged to separate the serum (the clear yellowish

*Continued*

fluid obtained upon separating whole blood into its solid and liquid components). Data obtained from the serum were used to construct concentration-time curves to evaluate the effectiveness of the substance on the growth of fungal protein. Comparisons between the species used were made and assessed against data from previous studies. The researchers concluded that integrating the pharmacokinetics data from the different animals used would result in better predictions for the way the sordarin derivatives are metabolised in humans and therefore contribute to the study design of initial clinical trials in humans.

* This is an example of animal research that has been published in a peer-reviewed journal. Details relate to this specific example and should not be taken to represent a 'typical' animal experiment. It is important to note that individually published experiments usually form one part of a continuing area of research, and the significance of the results may therefore be difficult to interpret.

## Summary

8.42 Pharmaceutical research and development has been transformed over the past 50 years because of the availability of advanced information and diagnostic technologies, and an increased understanding of genetics. At present a wide range of advanced methods that do not involve animals is used together with animal research. Although there has been a substantial decline in the total use of animals, pharmaceutical research remains responsible for a significant proportion of the animal experiments conducted in the UK each year. A very wide range of basic and applied medical and veterinary research projects is supported or conducted by pharmaceutical companies as part of the search for new medicines and vaccines for use in humans and animals. We described eight different stages in the development process. The majority of animals (60-80%) are used in the characterisation of promising candidate medicines; less (5-15%) are used in the preceding discovery and selection process. GM mice are most commonly used in the early stages of development of new medicines to assess the importance of a drug target, although they are also used increasingly in later stages (target validation) or as animal models of a disease (see Chapter 7).

8.43 The welfare implications for animals involved in research are as varied as the research itself. Non-experimental factors, such as housing, husbandry and the training of those handling the animals, especially in relation to the implementation of Refinements, all influence welfare. Some techniques, such as methods for administering a medicine and measuring the level in blood, are generic for all types of research. In the case of specific animal models of disease, welfare implications depend on the symptoms of the disease. A special case is the production of vaccines. Since the exact quality of biological products is often very difficult to control, tests to assess potency and toxicity are carried out on each batch, which may lead to symptoms ranging from lack of appetite to paralysis for animals such as monkeys, mice and guinea pigs.

8.44 The use of animals in pharmaceutical research and development in the future is difficult to predict. The following are among the many possible outcomes:[47]

- the use of animals may continue to fall as the use of advanced methods increases;
- the use of animals may remain static, but advanced imaging, sensing and biomarkers will allow extraction of even more information in an increasingly refined way; or
- the use of animals may rise because the increasing volume of information from the early stages of drug discovery presents the possibility of more and more new medicines.

47 See ABPI (2001) *Statistics, Animal Research and Development of Medicines*, available at: http://www.abpi.org.uk/publications/briefings/40301-ABPI-Brief-Statistics.pdf Accessed on: 2 May 2005. Various sources suggest that the use of animals is falling when compared with research and development activity undertaken by the largest pharmaceutical companies (see Samuels G (2003) *Medicines: Tried And Tested - In Animals?*, available at: http://www.abpi.org.uk/publications/publication_details/mttur/mttur_ani.asp; GlaxoSmithKline (2002) *The Impact of Medicines: Corporate and Social Responsibility*, available at: http://www.gsk.com/financial/reps02/CSR02/GSKcsr-10.htm#ref), or that the numbers of animals used may vary from year to year (AstraZeneca (2003) *Animal research*, available at: http://www.astrazeneca.com/Article/11174.aspx). All accessed on: 2 May 2005.

# Chapter 9

## Animal use in toxicity studies

# Animal use in toxicity studies

## Introduction

9.1 In this chapter we describe the purpose and principal methods of toxicity studies. Most of these studies are conducted to assess the degree to which substances are toxic (poisonous) for humans, animals or the environment, to investigate the mechanism of toxic chemicals, or to develop new or improved tests for specific types of chemically induced effects. We begin by explaining the scientific rationale behind important types of studies. These include: examination of adverse effects that may occur on first exposure to a single dose of a substance (acute toxicity studies), studies that seek to assess the potential of substances to interact with genetic material (genotoxicity), tests that aim to identify whether toxicity occurs after continuous exposure to a substance (repeated-dose toxicity studies), tests that are undertaken to find out whether cancers may develop as a result of exposure to certain chemicals, and studies to ensure the safety of medicines.

9.2 In the second part of the chapter we discuss a range of welfare implications that may arise for animals involved in toxicity testing. We consider first effects that may result from the dosing and sampling methods that are commonly used, and then effects related directly to the toxicity of the chemical that has been administered. Toxicity studies are highly variable in design, and where they involve the use of animals the implications for animal welfare must be considered on a case by case basis. We concentrate here on the more standardised animal methods that are widely used to characterise the adverse effects of chemicals on human and animal health, and on the environment. Many of the tests described are also used in the testing of medicines. For the most part we do not differentiate in the description between these different purposes.

### Box 9.1: Toxicity studies – number of animals used

Procedures for toxicological purposes accounted for 16 percent of all animal procedures undertaken in 2003 in Great Britain. Approximately ten percent of all animal procedures were carried out for pharmacological safety and efficacy studies.

About 13 percent of all animal procedures were toxicological tests conducted to conform to legislative or regulatory requirements.

Source: Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (London: HMSO).

## The current approach

9.3 The vast majority of toxicity testing is carried out in the context of regulatory requirements governing particular types of chemical in different parts of the world (see paragraphs 13.49–13.51). Regulatory bodies often emphasise the necessity of toxicity tests to preserve current levels of human health and environmental protection.[1] Notification of all new chemicals placed on the EU market for the first time must be given to the competent authorities of the Member States.[2] The EU is currently considering a proposal for a Regulation concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) which would require large numbers of existing chemicals to be evaluated for safety. Reach would be binding for all Member States (Box 9.2). Separate European Directives specify requirements for animal testing in the authorisation or licensing of plant-protection products, biocides and pharmaceuticals (see paragraphs 13.49–13.51). In other

1 European Commission (2004) *Opinion of the Scientific Committee on Toxicity, Ecotoxicity and the Environment on The BUAV-European Coalition to End Animal Experiments Report: The Way Forward - Action to End Animal Toxicity Testing*, available at: http://europa.eu.int/comm/health/ph_risk/committees/sct/documents/out217_en.pdf. Accessed: 26 Apr 2005.

2 The information that must be supplied by a manufacturer is laid down in the Dangerous Substances Directive (67/548/EEC), implemented in the UK by the Notification of New Substances Regulations 1993.

cases, for example for cosmetics and cosmetic ingredients, testing requirements are not specified in regulations but there is a general requirement for safety, which could be met by the use of animal or non-animal tests. National authorities in the EU issue guidance on how the provisions laid out in the Directives should be met, which, due to preferences of regulators, usually means that data from established animal tests must be provided. So as to maximise returns, many chemicals are marketed worldwide, and testing must then conform to the requirements of other regulatory bodies, particularly those of the USA and Japan.

9.4 Current testing regimes have evolved significantly over the past three decades. Existing practices have changed and new methods have been added. A major influence on these developments has been the Test Guidelines Programme of the Organisation for Economic Cooperation and Development (OECD), which has developed standardised methods of testing that are accepted in principle by all 30 OECD Member Countries[3] through an agreement on the mutual acceptance of data.[4] The OECD approach has largely removed the need for testing according to different protocols to satisfy regulatory authorities in different countries, and has thus substantially reduced the total number of animals used for certain standard tests. It also provides a focus for the introduction of new methods that replace, reduce or refine animal use. Change and revision have been slow but there are many current initiatives, within both the scientific and regulatory communities, that challenge present practice with the aim of providing the same or even better levels of human safety while using fewer animals (see Box 2.4 and paragraph 11.10). The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) also seeks to standardise the approach to testing of pharmaceuticals (see paragraphs 12.8, 13.50 and 15.84).

### Box 9.2: The EU REACH Initiative: Registration, Evaluation and Authorisation of Chemicals

Registration, Evaluation and Authorisation of Chemicals (REACH) refers to the new EU regulatory framework for chemicals proposed by the EC in October 2003. At the time of writing, the proposal is being considered by the European Parliament and the Council of the EU. The legislation is intended to bring 30,000 chemicals manufactured within or imported into the EU under a single regulatory regime. REACH aims to make manufacturers responsible for the chemicals that they produce and to make it easier for highly toxic chemicals to be removed from the market. Under the new system, businesses that manufacture or import more than one tonne of a chemical substance each year would be required to register it in a central database.*

The European Commission has stated that new legislation is necessary due to the inadequacy of the current legislative framework for chemicals. A particular problem concerns the arbitrary cut-off date in 1981, which provides the distinction between 'new' and 'existing' chemicals. At present, 'new' chemicals that have been placed on the market after 1981 must be tested if their production exceeds 10 kg per year, whereas there are no such provisions for 'existing' chemicals. Therefore, it is argued, the current legislation encourages the continued use of untested existing chemicals because it is easier and cheaper.†

REACH has proved controversial, not least because its requirements will result in a substantial increase in the number of animal experiments. Many chemicals have been in use for decades and there is concern that some tests may duplicate those already performed by private companies. The UK Government is advocating a policy of 'one substance-one Registration', as a means of minimising animal testing and reducing costs and bureaucracy. This means that companies would be required by law to share data on tested substances, in the hope that universally available data will avoid duplicate testing of that substance.‡

* See EC Enterprise and Industry (2005) *The New EU Chemicals Legislation – REACH*, available at: http://europa.eu.int/comm/enterprise/reach/overview.htm.. Accessed on: 3 May 2005.

† EC (2003) *Q and A on the new chemicals policy REACH*, available at: http://europa.eu.int/rapid/pressReleasesAction.do?reference=MEMO/03/213&format=HTML&aged=0&language=EN&guiLanguage=en. Accessed on: 27 Apr 2005.

‡ See House of Commons Science and Technology Committee (2004) *Within REACH: The EU's New Chemicals Strategy* (London: TSO), available at: http://www.publications.parliament.uk/pa/cm200304/cmselect/cmsctech/172/172.pdf. Accessed on: 3 May 2005.

3 Member Countries include the UK and other European Countries, Japan and the USA, a list is available at: http://www.oecd.org/document/58/0,2340,en_2649_201185_1889402_1_1_1_1,00.html. Accessed on: 26 Apr 2005.

4 OECD (2001) *Mutual Acceptance of Data (MAD)*, available at http://www.oecd.org/document/41/0,2340,en_2649_201185_1890473_1_1_1_1,00.html. Accessed on: 26 Apr 2005.

9.5 Toxicity has two main components: the effect caused and the level of exposure (dose) at which the effect is observed. Some tests are designed specifically to detect a particular effect (such as skin and eye irritancy, skin sensitisation and mutagenicity studies). Other tests (such as sub-chronic and chronic studies) are designed to detect a wider range of less-specific effects on organs or body systems and the dose range over which the effect develops.

9.6 Information from toxicity tests is first used to provide a classification for a chemical, for example to assign appropriate warning labels for containers, and, where necessary, for selecting measures, such as protective equipment, during manufacture, exposure and use. Data from tests that characterise the relationship between dose and toxicological response are integrated with information on human exposure to produce a risk assessment, and to identify control measures necessary to manage and reduce any identified risk. Tests on species such as fish and amphibians are used in a similar way to assess the potential environmental effects of chemicals. For pharmaceuticals, results from animal tests are used in combination with data on the efficacy of a potential medicine to decide whether the beneficial effects of the treatment would outweigh the risks of adverse side effects, and to establish a safe dose for use in clinical trials (see paragraphs 8.26–8.28). They may also indicate potential side effects that must be monitored carefully.

9.7 The prediction of the likely effects of chemical exposure on human health is based primarily on the results of tests involving experimental animals. The number of animals involved in these tests varies. A full complement of toxicity tests for a successful pharmaceutical compound that proceeds to the market, involving single dosing, repeat sub-chronic and chronic dosing, reproductive testing, genotoxicity and carcinogenicity testing, can involve between 1,500 and 3,000 animals. The actual numbers required will depend on the need for further tests according to the nature of the test substance and also its toxic properties. The numbers of animals used to test other types of chemical are generally lower, but in some cases, where there is particular controversy about the safety of a chemical, tests may be repeated, with modifications, resulting in the use of even more animals.

9.8 Large numbers of animals are also used in several other tests. For example, a carcinogenicity bioassay generally involves 800 animals in total (400 of each sex) and may be conducted on both rats and mice. Adult animals (typically at least 80 animals of each sex per study), offspring and fetuses are used in reproductive and development studies. Rats and mice are most commonly used (74 percent), but in some cases testing is carried out on other animals such as rabbits (four percent), guinea pigs (three percent), dogs (one percent) or primates (less than one percent).[5] The interpretation of the results for assessing human safety depends on a number of assumptions. First, unless there is specific knowledge of species differences in the test response, it is assumed that the effects detected in rodents or other species are the same as those that would be induced in humans. Secondly, it is assumed that the sensitivity of the test animals represents, at best, the average sensitivity of the highly heterogeneous human population and that for some members of the human population the health risk could be much higher (see paragraph 8.39, Box 9.3 and paragraph 10.33). We consider next a range of examples to illustrate the different kinds of toxicity tests which are currently used.

5 Figures refer to percentages of procedures started in 2003 and carried out for the purpose of toxicology or safety and efficacy evaluation. See Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (Norwich: HMSO).

### Box 9.3: Sources of uncertainty in animal toxicity tests

Commentators who are critical about the reliability of toxicity tests carried out in animals with regard to predicting toxic effects in humans observe that the following factors may influence transferability:*

- species, strain and gender variations may affect extrapolation to humans;
- scaling from small, short-lived animals (usually rodents) and large doses, to large, long-lived animals (humans) and usually smaller doses may pose problems;
- there may be variability due to different dosing routes and extrapolation to human exposure;
- test animals usually constitute a homogeneous (genetic and otherwise) population, whereas there are often significant differences between humans, which may affect, for example, drug metabolism;
- there are pragmatic limitations with regard to testing chemical mixtures or interactions between chemicals; and
- the dose required to produce toxic effects in animals may never be reached in humans.

Researchers carrying out toxicological tests acknowledge that these factors need to be taken into account. They observe that, provided they are considered appropriately in making extrapolations, animals can be useful models for the prediction of toxic effects in humans (see paragraphs 10.27–10.36).†

* Langley G (2004) *Chemical Safety and Animal Testing: A regulatory smokescreen?* A BUAV Report (London: BUAV), available at: http://www.buav.org/pdf/Smokescreen.pdf. Accessed on: 4 May 2005.

† Association of the British Pharmaceutical Industry *(2001) Submission to the House of Lords Committee on Animals in Scientific Procedures*, available at: http://www.abpi.org.uk/information/industry_positions/011126.asp. Accessed on: 4 May 2005.

## Principal types of animal-based toxicity tests

### *Acute toxicity*

9.9 Acute toxicity refers to the adverse effects that occur on first exposure to a single dose of a substance. Separate tests are needed to detect the effects of contact with the skin and eye (corrosion, irritancy and sensitisation; topical or local toxicity) and the effects on internal organs of a substance that is swallowed, inhaled, absorbed through the skin or injected (systemic toxicity; see paragraph 9.28).

9.10 In the case of local toxicity, skin irritancy is normally assessed by applying the test substance to shaved areas of the backs of rabbits and observing the development of redness, swelling, erosion and ulceration over a period of 72 hours (see paragraph 9.36). Eye-irritancy tests involve administering the test substance directly into the eye of the rabbit and observing corneal opacity, swelling, reddening and other signs of irritation.

9.11 In the case of skin-sensitisation testing, multiple doses of the test substance are applied to the skin of guinea pigs to see if a later dose will cause a strong immune reaction, indicating sensitisation to the chemical (see paragraph 9.36). Tests using guinea pigs are increasingly being replaced by a test involving mice called the local lymph node assay. The test material is applied to the ears of the mice. After an interval the mice are euthanised and the early stages of sensitisation are detected by measuring the level of induced DNA synthesis in the lymph nodes. This test provides more useful information, uses fewer animals than the guinea pig test, and causes substantially less pain and distress to the animals involved.

9.12 The main purpose of skin and eye testing is to allow classification and labelling of corrosive, irritant and sensitising chemicals. The current systems of classification now follow a progressive, step-wise strategy that allows chemicals to be classified as corrosive or irritant to the skin by using physico-chemical properties, such as pH value. Tests that use isolated human or animal tissue cells or *ex vivo* tissues or organs to identify chemicals with the potential to cause severe irritation or corrosion are known as non-animal pre-screens (see paragraph 11.9). For sensitisation, analysis of chemical structure (structure–activity relationships) can identify many potential sensitisers. Therefore, in many cases it is now possible to classify chemicals without the need for animal tests. The value of these

approaches is illustrated by a decrease in rabbit eye tests in the UK from approximately 4,000 in 1995 to 1,100 in 2003.[6]

9.13 Acute systemic toxicity is assessed by the administration of a single dose of compound, typically to rats and mice, orally, dermally or by inhalation. For pharmaceuticals, the main aims of these studies are to determine the nature (including delayed toxicity) and duration of any acute toxic response. They also determine the maximum non-lethal dose and provide preliminary information relevant to single exposure or over-dosage in humans (see paragraph 9.39).[7]

9.14 For industrial chemicals and agrochemicals, testing covers acute toxicity by oral, dermal and inhalation routes of exposure. The information obtained is used primarily to ascribe a chemical to bands of acute toxic effect, which restricts how the materials may be used, and thus the extent of human exposure by the routes of exposure which have been evaluated. In the past, in the UK and elsewhere, acute systemic toxicity was investigated by the use of lethal-dose tests, in which the oral dose causing the death of 50 percent of the treated animals (the $LD_{50}$ value) was determined.[8] Such tests used at least 30 animals per test chemical and required death of the animals as an endpoint, regardless of the suffering caused. In 2001 the OECD agreed that the $LD_{50}$ test for acute oral toxicity should be abolished and deleted from the OECD manual of internationally accepted test guidelines by the end of 2002 (see paragraphs 9.4 and 12.8).[9] Several alternative methods have been developed which use fewer animals and in some cases replace death as the endpoint with signs of significant toxicity instead. Information on similar chemicals is used to guide the selection of initial dose levels and the tests are designed to avoid or minimise lethality or severe toxicity. These methods have replaced the $LD_{50}$ test for acute oral toxicity, but several acute tests such as those involving inhalation, dermal and eye exposure have yet to be modified. They are still used internationally for tests on birds and, for some purposes, also on mammals.[10] Lethal-dose tests are also still used to assess the safety of biological products, such as vaccines (Box 8.5), and certain foods, such as shellfish, for the presence of toxins (see paragraph 9.37).

9.15 The approach to assessing the acute toxicity of pharmaceuticals differs from that described above, in that maximum tolerated dose (MTD) studies are carried out to aid the later process of dose selection. These tests often replace acute studies, especially in the case of larger species such as the dog and primates which are used to complement and verify earlier findings in rodents. They involve steadily increasing the dose given to an animal (single or a number of consecutive doses), until adverse effects indicate that an MTD has been reached. This is normally determined by careful observation of the animals, but there is no universally accepted definition of the MTD and effects such as vomiting and convulsions may occur and are sometimes used as signs of the MTD (see paragraphs 9.34–9.45).

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6 See Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (Norwich: HMSO).

7 The studies provide information that may support selection of dose levels for repeated-dose toxicity studies, *in vivo* genotoxicity tests (see paragraphs 9.20-9.21) and, subsequently, first human exposure studies.

8 The OECD gives the definition as the dose that can be expected to cause death in 50 percent of animals when administered by the *oral* route.

9 OECD (2001) *OECD Test Guideline 401 will be deleted: A Major Step in Animal Welfare: OECD Reaches Agreement on the Abolishment of the $LD_{50}$ Acute Toxicity Test*, available at: http://www.oecd.org/document/52/0,2340,en_2649_34377_2752116_1_1_1_1,00.html. Accessed on: 27 Apr 2005; The UK ceased the practice of the $LD_{50}$ test in 1999 (APC (1999) *Press release: LD 50 Test - Changes To Licensing Procedures*, available at: http://www.apc.gov.uk/press_releases/991021.htm. Accessed on: 27 Apr 2005). In the US, Environmental Protection Agency guidelines describe the $LD_{50}$ test as standard for pesticides and toxic substances although state that it may be unnecessary in certain circumstances (Environment Protection Agency (1998) *Health Effects Test Guidelines OPPTS 870.1100 Acute Oral Toxicity*, available at: http://www.epa.gov/docs/OPPTS_Harmonized/870_Health_Effects_Test_Guidelines/Series/870-1100.pdf. Accessed on: 27 Apr 2005.

10 OECD (2002) OECD guidelines for the testing of chemicals: Proposal for a new guideline 223 – Avian acute oral toxicity test, available at: http://www.oecd.org/dataoecd/16/41/1836204.pdf. Accessed on: 27 Apr 2005.

***Repeated-dose toxicity studies***

9.16 These studies have three main objectives (i) to identify toxicity that develops only after a certain length of continuous exposure to the chemical, (ii) to identify the organs most affected and (iii) to determine the doses at which each effect occurs.

9.17 Repeated-dose studies are conducted for various periods of time. The 28-day (sub-acute) study is most common, but studies of 90 days to one year are also regularly carried out. Rats and mice are generally used but for certain classes of chemicals, such as agrochemicals and pharmaceuticals, the tests may also be conducted in non-rodent animals such as the beagle dogs, pigs, marmosets or macaques (see paragraphs 9.26 and 9.30). The test data allow an assessment of the highest dose without significant effects (the 'no observed adverse effect level', or NOAEL). This is used in risk assessment and risk management, by limiting the acceptable exposure of humans to a fraction of the NOAEL. For example, in the case of agrochemicals and food additives, these studies are used to assign a reference dose to which safety factors are applied to give an acceptable daily intake (ADI) that is typically a hundredfold less than the observed NOAEL. This can be defined as the dose level to which humans may be exposed, through residues on foodstuffs and in drinking water, with the practical certainty that no adverse health effects will ensue.

9.18 Repeated-dose studies are also used to give an insight into any species differences in toxicity that could be relevant to the assessment of risk in human health. Depending on the use and physico-chemical properties of a chemical, different routes of administration, such as oral, by inhalation or dermal contact, may be used to give a more appropriate risk assessment. For pharmaceuticals, results of these studies support investigations requiring the first administration of the test substance to humans.

***Carcinogenicity***

9.19 For the assessment of carcinogenicity, rats and mice are dosed for up to two years (the typical lifespan for these species) and the incidence and type of the tumours that develop is evaluated (see paragraph 9.33). This knowledge is used to assess the risk of cancer induction by the chemical in exposed humans. In practice, the assessment of repeated-dose studies and carcinogenicity is often combined into a single study in rodents thus reducing the use of experimental animals.

***Genotoxicity***

9.20 Short-term studies investigating interactions with genetic material (DNA and chromosomes) are widely used to screen chemicals for the potential to cause cancer or heritable mutations. Most of these studies involve the use of *in vitro* assays for mutation in bacteria or isolated mammalian cells that have been shown to predict the potential for a substance to be carcinogenic or mutagenic through interaction with DNA. In the pharmaceutical industry tests are performed as high-throughput screens (see paragraphs 8.9 and 8.21), both early in drug discovery and also to support drug registration. Animal studies, usually in the mouse, are used only when one or more of these *in vitro* tests has given a positive result, and with the purpose of demonstrating that the chemical can or cannot reach a sensitive tissue and cause genetic changes in the intact animal. In practice, very few chemicals that have been confirmed to be mutagenic *in vitro* are tested any further in animals. However, in the case of pharmaceuticals, regulatory requirements demand that an *in vivo* test be completed before the start of Phase II clinical studies in humans.

9.21 *In vivo* tests include the rodent bone marrow micronucleus test, which is an early predictor of carcinogenic activity. A single dose of compound is administered to rats or mice which are killed either 24 or 48 hours later for examination of chromosomal changes in bone marrow

cells. It is expected that the highest dose level used will show evidence of adverse effects if the substance is genotoxic, and the MTD is normally used to set this dose level.

***Effects on reproduction and development***

9.22 Studies within this category are intended to determine the effects of compounds on various aspects of the reproductive capacity of the adult, and on the development of the offspring. The most comprehensive test method for reproduction (the two-generation reproduction study) involves repeated oral doses to young rats through the period of sexual maturation into young adulthood when the animals are mated to treated females. The females are dosed throughout pregnancy and until the offspring are weaned. The pups are dosed until adulthood and mated and the second-generation young evaluated. These tests provide information on fertility, mating behaviour, parental behaviour and development of the neonate to adulthood. The results are used in hazard classification and in risk assessment. More-limited information on fertility and reproductive performance can also be obtained from a one-generation study or a screening test, which combines reproductive investigations with a 28-day repeated-dose toxicity test.

9.23 Studies on developmental toxicity provide specific information on the potential hazards to the unborn that may arise from exposure of the mother to a particular substance during pregnancy. Typically, groups of pregnant rats or rabbits are treated orally for up to the whole period of gestation, and the uterine contents are then examined and evaluated just prior to parturition. An evaluation is made of maternal toxicity relative to that in non-pregnant females, embryo or fetal death, altered growth and structural changes in the fetus. Rabbits are used in addition to rats and mice because rodents do not generally respond, or respond variably, to the effects of potent human teratogens such as thalidomide (see Box 8.4). The results of both tests are used in classification by hazard and in risk assessment.

***Safety pharmacology***

9.24 In the development of pharmaceutical products, additional tests are needed to detect exaggerated intended or unintended pharmacological responses. Pharmacology studies to evaluate safety are generally conducted in the dog (for cardiovascular endpoints) and in the rodent (for assessment of the effect on the whole body). Some examples of the types of studies performed in animals are described briefly below (see Box 9.4).

- **Dog telemetry:** dogs are implanted with radio-transmitters for continuous monitoring of blood pressure, heart rate, body temperature and electrocardiogram (ECG, see paragraph 4.56). These parameters can be monitored from the conscious dog, and allow the measurement of the effects of test compounds on the cardiovascular system *in vivo*. Dogs are usually reused in multiple studies, subject to veterinary and regulatory approval by the Home Office. They are euthanised at the end of the studies.
- **Haemodynamics of anaesthetised dogs:** this type of research is undertaken as a follow-up to dog telemetry. Under terminal anaesthesia, multiple systems may be investigated including, for example, blood pressure, heart rate, ECG and peripheral blood flows (also coronary and renal blood flows).
- **Absorption, distribution, metabolism and excretion studies (ADME):** although not strictly toxicity studies, these investigations (typically undertaken in rodents and dogs) are used to assess the amount of chemical or pharmaceutical that is absorbed into the animal, where it is distributed within the body, how it is changed by metabolism, the time-course for these events and how, and at what rate, the material is eliminated from the body (see paragraph 9.31). This information is used to select dose levels for toxicity studies and

clinical trials, to identify compounds for further development, to interpret toxicity data, and in risk assessment (see paragraphs 8.10–8.11).

- **'Balance' studies:** in these studies radiolabelled doses are given to intact or surgically prepared animals and samples including blood, bile, urine, faeces and expired air are collected to determine the processing of the drug-related material, and to investigate its absorption and possible retention.
- **Pharmacokinetic studies:** studies are conducted for pharmacological and toxicological evaluation of candidate drugs to characterise their pharmacokinetic behaviour, usually after intravenous and oral administration, although other routes may also be used (see paragraphs 8.20–8.26). This information is used to support the more limited sampling performed in toxicity studies, to fully characterise the pharmacokinetics in animals and to predict the pharmacokinetics in humans, which assists in estimating the likely human dose.

### Box 9.4: Example of research – testing species differences in the toxicity profile of an approved herbicide (currently in use)

Lappin GJ, Hardwick TD, Stow R *et al*. (2002) Absorption, metabolism and excretion of 4-chloro-2-methylphenoxyacetic acid (MCPA) in rat and dog *Xenobiotica* **32**(2): 153–63.*

This research investigated differences between rats and dogs in the toxicity of a herbicide, MCPA. This chemical is used to control a wide variety of broad-leaved weeds in many crops as well as non-crop areas. A radioactive version of the herbicide was fed to the rats and dogs.

Twenty rats between six to eight weeks old and four beagle dogs between six and 12 months of age were used, obtained from suppliers of laboratory animals in the UK.

Two groups of rats were administered single doses of the herbicide at different levels by gavage (feeding by means of a stomach tube, see paragraph 9.28). Half the rats were group-housed in the period following dosing and a sample of their blood was taken on ten occasions. The remaining rats were housed individually, and their urine and faeces were collected for seven days.

For all four dogs a single dose was administered by capsule, followed by a second single dose at a higher concentration four weeks later. All four dogs were housed individually for five days following dosing, during which time their blood was sampled at 11 time points, and samples of urine and faeces were collected.

Signs of toxicological response to this compound had previously been shown to include reduced weight gain, increased kidney weight and altered clinical chemistry in the rat. The effects in the dog were more severe with clear hepatotoxicity (having a damaging effect on the liver), anaemia and severe renal toxicity. The highest dose given in this procedure resulted in mild toxicological effects in the rats. The responses in dogs were described as being beyond the MTD if repeated exposures at this level had occurred.

The researchers found that MCPA did not accumulate in rat tissue. The results were less clear in the case of the dog as this species is more sensitive to the effects of MCPA. The authors reached the most probable physiological explanation for the species differences. They also investigated previous evidence that this type of compound may reach higher blood concentrations in males than females, and found that there were in fact no differences. For this reason the researchers went on to use only male dogs, rather than increase the number of dogs used. The authors state that the data add to a growing body of evidence showing that the dog is deficient in the excretion of weak organic acids, and that therefore this species is not appropriate for assessing the toxicological significance of this class of compound in humans.

* This is an example of animal research that has been carried out in the UK and published in a peer-reviewed journal. Details relate to this specific example and should not be taken to represent a 'typical' animal experiment. It is important to note that individually published experiments usually form one part of a continuing area of research, and the significance of the results may therefore be difficult to interpret.

### *Ecotoxicity*

9.25 All of the tests described above are carried out to assess the possible adverse effects of a substance on human health, but an increasing amount of testing is being done to investigate potential effects on the environment and wildlife. For example, large numbers of fish, and smaller numbers of birds and amphibians, are used to test industrial and agrochemicals for their toxicity to wildlife populations (see also Box 9.4).

## Issues concerning the welfare of laboratory animals in toxicity testing

9.26 We have commented on the numbers and types of animals most commonly used in toxicity testing (paragraph 9.8). We also observed that some toxicity tests may extend over several months or years in contrast to most animal experiments conducted for biomedical research. For rodents, age-dependent health problems, with concomitant stress, will usually occur with increased frequency towards the end of tests. Loss of animals can compromise study validity and confound the interpretation of data, especially from carcinogenicity studies.[11] This may sometimes encourage investigators to minimise animal loss by avoiding euthanasia as far as possible, which may result in increased pain and distress to the animals.

9.27 It is impossible to fully predict the pain and suffering that individual animals might experience during toxicity testing. However it is possible to assess the likelihood that pain and distress will occur under a particular set of conditions and exposures. The following aspects of toxicity testing can give rise to adverse consequences for the welfare of test animals, the extent of which depends on the test and species involved: (i) transport (see paragraph 4.36); (ii) housing and husbandry (see paragraphs 4.37–4.43);[12] (iii) dosing and sampling procedures (which might be repeated) (see paragraphs 4.49–4.52); (iv) the length of the observation period and (v) the toxic consequences of dosing. The adverse effects on animals that may arise specifically in toxicity tests, as opposed to other forms of animal research, are due mainly to dosing procedures and the toxic effects of the treatments.[13]

9.28 Dosing can involve the repeated administration of test material by a variety of routes of exposure, including gavaging (stomach intubation or forced feeding), injection, skin painting and inhalation. Some types of administration are likely to be very stressful to animals, especially when they are repeated and are of relatively long duration (see paragraphs 4.45 and 9.28). In addition, dosing into the eye and inhalation exposure involve restraint for several minutes or hours.

9.29 The right choice of dosing vehicle and volume is an important means of refining toxicity tests from both scientific and welfare perspectives. This is particularly so regarding the maximum amounts that should be administered to the eye and orally by gavage.[14] The use of low dosing volumes is a very effective way of reducing stress during topical ocular administration. Thus, the traditional dosing volume of 0.1 ml can be reduced by a factor of 10 or even 20 in eye-irritation studies. During gavaging, volumes of 1–50 ml/kg are usually administered, depending on the species being used. The administration of large volumes through this route can modulate the patterns of absorption, thereby affecting toxicity. For example, volumes nearing or exceeding the stomach volume will result in the delivery of some of the substance to the small intestine.

9.30 Stress can also be induced by physiological changes accompanying oral dosing. For example, alterations to gastric secretion and motility, as well as increases in heart rate and blood pressure, can occur. There can also be changes in biochemical parameters, such as levels of

11 Roe FJC (1993) Influence of animal species, strain, age, hormonal, and nutritional status, in *Experimental Toxicology, The Basic Issues*, 2nd Edition, Anderson D and Conning D (Editors) (Cambridge: The Royal Society of Chemistry), pp23–34.

12 Morris T, Goulet S and Morton D (2002) The international symposium on regulatory testing and animal welfare: recommendations on best scientific practices for animal care in regulatory toxicology *ILAR J* **43**, Supplement: S123–5; Hawkins P, Morton DB, Bevan R *et al.* (2004) Husbandry requirement for rats, mice, dogs and non-human primates used in telemetry procedures Seventh Report of the BVAAWF/FRAME/RSPCA/UFAW Joint Working Group on Refinement, Part B. *Lab Anim* **38**: 1–10.

13 Stephens ML, Conlee K, Alvino G and Rowan AN (2002) Possibilities for refinement and reduction: future improvements within regulatory testing *ILAR J* **43**, Supplement: S74–9.

14 Brown AP and Levine BS (1999) *Relationship Between Dosing Vehicles, Dose Volume, and Stress*. Report prepared for the US National Toxicology Program Unpublished report.

stress hormones. Furthermore, under conditions where animals are fed in laboratories *ad libitum*, as is the usual situation, gavaging of large volumes may result in aspiration of the test substance due to the presence of food in the stomach and duodenum. The volume of the gastrointestinal tract for receiving administered material is reduced and injury to the lungs may ensue. Recent research showed that gavaging rats with corn oil, but not the test substance or water, resulted in stress which was volume-dependent, as manifested by corticosterone levels (a hormone released in response to stress).[15] The authors recommended that dosing volumes for rats should not exceed 10 ml/kg. It is important to consider this information in the light of other best-practice guidelines on dosing.[16] At the same time, views differ as to how widespread the gavaging of large volumes *ad libitum* is in practice, and some researchers comment that significant steps have been made to refine the method.[17]

9.31 In metabolism studies, animals are housed in metabolism cages and might have external tubes implanted into their bile ducts.[18] During toxicokinetic studies in dogs, it is not unusual for the same animals to be reused after a suitable period of time, as such animals are thought to suffer less stress than those used for the first time.

***Effects due to toxicity***

9.32 The usual practice in toxicity testing is to induce overt toxicity in some animal groups, in order to ensure that, where toxicity is not observed in other exposed groups, the effects are not due to any inherent defect in the methodology. Thus, some form of harm to animals is an integral part of animal-based toxicity testing and is viewed by those conducting such tests as being unavoidable to achieve the scientific objectives of the work.

9.33 Toxicity can arise from reversible or irreversible effects, and can affect a range of different organs to different degrees. The adverse effects of substances on animal physiology can range from minor changes, such as reduced weight gain, small physiological alterations or changes in the levels of circulating hormones, to severe effects such as organ function loss (a major cause of acute toxicity), leading to death. Intermediate levels of toxicity, such as those destroying tissue and adversely affecting tissue function, could result in pain and suffering. Similarly, the development of tumours during carcinogenicity testing, or intestinal swelling during sub-chronic or chronic testing, might also lead to pain and discomfort.

9.34 The adverse effects which are used to define the MTD range from the very mild, which include non-clinical signs of lethargy or effects on weight, to the more substantial, such as convulsions. For example, various tests of toxicity often require signs to be scored, such as changes in the condition of the coat and eyes, as well as other signs of ill-health. Many of these conditions might be expected to reflect pain and suffering to differing degrees.

9.35 There is general confusion among toxicologists as to exactly what defines an MTD, 'severe distress', 'obvious pain', a 'moribund condition' and other descriptions of animal welfare. Some have argued that the relevant OECD test guidelines need to be revised accordingly.[19] Several of the OECD test guidelines are vague on issues such as environmental enrichment, where for example group housing is not specified when it would be possible.[20] All these

15 Brown & Levine (1999) ibid.

16 Morton DB, Jennings M, Buckwell A *et al*. (2001) Refining procedures for the administration of substances *Lab Anim* **35**: 1–41.

17 See, for example: Brown AP, Dinger N, Levine BS (2000) Stress produced by gavage administration in the rat *Contemp Top Lab Anim Sci* **39**:17-21.

18 Gangolli SD and Phillips JC (1993) The metabolism and disposition of xenobiotics, in *Experimental Toxicology, The Basic Issues*, 2nd edn, Anderson D and Conning D (Editors) (Cambridge: The Royal Society of Chemistry), pp130–201.

19 Koeter HBWM (1999) The OECD Test Guidelines Programme and animal welfare concern: how to avoid major animal suffering, in *Humane Endpoints in Animal Experiments for Biomedical Research*, Hendriksen CFM and Morton DB (Editors) (London: Royal Society of Medicine Press), pp13–14.

ambiguities can act as potential sources of avoidable suffering for the animals.

9.36 Other examples of toxicity endpoints that are likely to be painful and stressful include skin irritation and corrosion where single doses are applied to shaved areas of the backs of rabbits. Exposure can extend over four hours, and the animals may experience ulceration of the skin as well as swelling and itching. In sensitisation testing, multiple dosing is practised, and in addition to the above signs, the skin may crack and peel. Other signs that can be observed during acute, sub-acute and chronic toxicity testing include both external and internal bleeding, diarrhoea, loss of appetite, vomiting (in non-rodents), aggression, salivation, changes in blood pressure, coma, convulsions, lateral recumbency and tremors, loss of fur and hair, dehydration, or nasal discharge. Some of the less drastic effects of toxicity can arise merely from the act of dosing.

9.37 Very severe adverse effects can become manifest extremely rapidly as a result of neurotoxicity following dosing. For example, during the mouse bioassay for diarrhoetic shellfish toxins, atypical results[21] can arise which cause rapid death, following signs of substantial distress from shock and extensive trauma, accompanied by violent and rapid leg and body movements and agonal breathing (abnormal and uncertain respiration often characterised by gasping for breath), collapse and finally death from heart failure.[22]

***General observations concerning the assessment of animal welfare in toxicity studies***

9.38 It is difficult to assess accurately either the individual or the collective burden of suffering that is sustained by animals used in toxicity testing. Many toxicity procedures do not usually result in more than some discomfort to most of the animals concerned, at least in the case of rodents. Moreover, only certain test groups of animals will be subjected to tests leading to overt signs of toxicity during an experiment. These groups of animals comprise the concurrent positive controls (animals treated with a chemical known to have adverse effects as a comparator on the sensitivity of the test substance) and those animals that receive high doses in dose-response studies. However, in such cases it is likely that significant pain and distress could result, depending on the type of toxicity elicited. All animals used in toxicity testing are routinely killed immediately at the end of experiments for examination (see paragraphs 3.47–3.49).

9.39 The fact that animals can suffer stress during toxicity testing has been investigated in studies in rats by assessing stress and discomfort from clinical and pathological observations.[23] A substantial proportion of the animals suffered from serious discomfort, with some having obvious clinical signs, such as impaired locomotion and anaemia. Most of these animals only displayed non-specific clinical signs and the development of humane endpoints was confounded. The difficulty of interpreting data where overt toxicity is induced can be exacerbated by the fact that dosing of very high levels of test material might be required, with accompanying adverse welfare consequences for animals, including death. Death as an endpoint in toxicity testing, particularly when caused by the above conditions (the administration of 'heroic' doses), can be a misleading indication of hazard, since it might well not reflect any direct biological effects of the test material. Rather, death in such

20 Combes RD, Gaunt I and Balls M (2004) A scientific and animal welfare assessment of the OECD health effects test guidelines for the safety testing of chemicals under the European Union REACH system. *ATLA* **32**: 163-208.

21 These effects are 'atypical' in the sense that they arise very rapidly, usually within minutes of administration of the toxin (in most other cases effects more commonly occur within a timespan of several hours).

22 Combes RD (2003) The mouse bioassay for diarrhetic shellfish poisoning: a gross misuse of laboratory animals and of scientific methodology *Alternat Lab Anim* **31**: 595–610.

23 Van Vlissingen JMF, Kuijpers MHM, van Oostrrum ECM *et al*. (1999) Retrospective evaluation of clinical signs, pathology and related discomfort in chronic studies, in *Humane Endpoints in Animal Experiments for Biomedical Research*, Hendriksen CFM and Morton DB (Editors), (London: Royal Society of Medicine Press), pp89–94.

circumstances can be due to indirect effects such as dehydration leading to a heart attack. Similar effects can be caused by starvation which might occur when food becomes unpalatable during dietary administration of the test substance.

9.40 It has also been stressed that the design of toxicity experiments should be related to the way in which the resulting experimental data are going to be used.[24] Thus, if it is intended to label a substance as hazardous on the basis of adverse reactions detected in one or a few animals, there is little point in subjecting additional animals to treatment and potential toxicity. The use of pilot studies in which the unknown effects of a treatment can be assessed in a few animals prior to conducting a full-scale experiment are also desirable in order to reduce numbers of animals used, and the potential suffering. This approach is, unfortunately, not routinely practised by toxicologists.

9.41 It is important that those who care for and subject animals to toxicity testing should become aware of the behavioural, emotional and physiological conditions and requirements of the animals (see paragraph 4.18). The ability of animals to anticipate negative events such as experimental procedures can increase anxiety levels and alter hormonal production which might also compromise the scientific quality of the data.

9.42 Several factors are expected to increase the numbers of animals being used in toxicity testing, as well as the severity of testing, including:

- the High Production Volume chemicals testing programme in the USA;[25]
- the new Registration, Evaluation and Authorisation of Chemicals (REACH) legislation in the EU[26] (see Box 9.2);
- pesticide regulations in the EU that require more-extensive testing;
- the development and attempted validation of several animal tests to screen chemicals for endocrine (hormone)-disrupting activity;[27] and
- the very substantial increase in the generation and utilisation of novel GM animal strains in toxicity studies.[28]

Effective implementation of the Three Rs in these areas is crucial (see Chapters 11 and 12).

9.43 Finally, it must be acknowledged that toxicity tests in laboratory animals have limitations as a means of identifying hazards for human health, and managing risks to human health (see also Box 9.3). The example given in Box 9.4 also shows that different species may respond differently to the same compound. It has been argued that such problems fundamentally undermine the scientific and ethical justification for using animals to assess chemical safety. We have considered these questions briefly in paragraphs 8.39–8.41 and return to issues raised by the scientific validity of using animals in Chapter 10.

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24 Morton DB (2002) The importance of non-statistical experimental design in refining animal experiments for scientists, IACUCs, and other ethical review panels, in *Applied Ethics in Animal Research: Philosophy, regulation, and laboratory applications*, Gluck JP, DiPasquale A and Orlans FB (Editors) (West Lafayette, IN: Purdue University Press), pp149–78.

25 Nicholson A, Sandler J and Siedle T (2004) An evaluation of the US High Production Volume (HPV) chemical-testing programme. A study in (ir)relevance, redundancy and retro thinking *ATLA* **32** Supplement 1: 335–41.

26 Combes R, Dandrea J and Balls M (2003) A critical assessment of the European Commission's proposals for the risk assessment and registration of chemical substances in the European Union *ATLA* **31**: 353–64.

27 Combes RD and Balls M (2003) How much flexibility is possible when validating new *in vivo* and *in vitro* toxicity test methods? *Alternat Lab Anim Exp* **31**: 225–32.

28 van Zeller A-M and Combes RD (1999) Transgenic mouse bioassays for carcinogenicity testing: a step in the right direction? *Alternat Lab Anim Exp* **27**, Supplement 1: 839–46.

## Summary

9.44 In this chapter we have surveyed the ways in which animals are used in safety assessments of compounds including medicines, household chemicals, agrochemicals and industrial chemicals. Various species are used, most commonly rodents and also larger animals including rabbits, dogs and primates. Chemicals (including potential medicines) are assessed for their potential to be hazardous to humans, and estimates of the risk of adverse effects from particular levels of exposure are produced. Most toxicity testing is undertaken in the context of legal and regulatory requirements governing the use of particular types of chemical in different parts of the world.

9.45 A range of tests are described including: inhalation, skin irritancy, genotoxicity, acute dosing, repeated dosing and effects on developing fetuses. We observed that a full complement of toxicity tests for a pharmaceutical compound that reaches the market usually involves between 1,500 and 3,000 animals. Adverse welfare effects may arise from the environment in which animals are kept, and may therefore depend on housing and handling conditions (see Paragraphs 4.37–4.47). Specific welfare implications resulting from toxicity procedures depend on dosing and sampling methods, and the effects of the chemical. While toxicologists emphasise that many procedures affect animals only in minor ways, certain groups of animals, especially those in the positive control group, will be subjected to tests leading to overt signs of toxicity during an experiment, which means that significant pain and distress could occur, depending on the type of toxicity elicited. We consider ways of replacing, refining and reducing these effects in Chapters 11 and 12. In the next chapter, we summarise the discussion presented in Chapters 5–9, and consider in particular arguments about the scientific validity of animal research.

# Chapter 10

## Summary of Section 2

# Summary of Section 2

10.1 Below we summarise the findings of Section 2, which concerned the scientific uses of animals and the implications for welfare in four different contexts: basic research (Chapter 5); animals as models for human disease (Chapters 6 and 7); pharmaceutical research and development (Chapter 8); and toxicity testing (Chapter 9). We also address more specifically issues which concern the transferability of results obtained from animal research to humans.

## Basic research (Chapter 5)

10.2 Basic or curiosity-driven research encompasses a wide range of behavioural, physiological, developmental and genetic studies. In Chapter 5 we described a number of experiments to show that animal research in this area extends from mostly observational to highly invasive experiments. Some research, such as the study of birdsong, is undertaken primarily to increase our knowledge of the animal kingdom (see paragraphs 5.2-5.3). Other areas of basic research seek to improve understanding about fundamental biological processes. Some of this knowledge may eventually lead to applications from which humans benefit directly.

### *Observational research*

10.3 Observational research on animals in their natural habitat is undertaken for purposes of conservation and in order to understand, for example, patterns of social interactions between animals. If conducted with care, it may not result in obvious adverse effects to the animals. The effects of behavioural studies undertaken in laboratory environments depend on contingent factors, such as transport, breeding, the standards of handling and husbandry and conditions of housing (see paragraphs 4.36-4.48 and 12.21) as well as on those that are determined by the experiment itself. We included the common example of mazes used to investigate aspects of rodent learning and memory (see paragraph 5.4). The actual experimental setting of these behavioural studies would normally be expected to cause the animals only relatively minor distress or suffering, if any. However, some behavioural studies include manipulations of the environment that make certain tasks more difficult or unpleasant for the animals. The welfare implications of such procedures depend on the degree to which the challenges are experienced as stressful by the animal.

### *Physiological studies*

10.4 Physiological studies involve surgical, dietary or drug treatments that are directed at understanding function at the physiological, cellular or molecular levels. These types of experiments have been undertaken in a wide range of research projects that contributed to current knowledge about human and animal biology, and medicine. Most of our knowledge about the endocrine (hormonal) system, the immune system and the nervous system (paragraphs 5.5-5.11) is based on research involving animals. Studies of the responses underlying graft rejection in immunodeficient rodents eventually facilitated the development of organ transplantation in humans (see paragraph 5.8). Research on immunodeficient rodents is now contributing to the understanding of the complex processes of diseases that affect the immune system, such as HIV/AIDS and other diseases (paragraph 5.9). With regard to welfare implications malaise is a common feature of infection in humans and animals, which both show slowed locomotion, poor appetite and abnormal body temperature. Sub-clinical infections may become clinical in immuno-compromised animals.

***Neurobiology***

10.5 Animal studies have also contributed to our knowledge of the human nervous system (see paragraph 5.11). Primates have been used in research aimed at understanding how complex brains work, as their neurological development and higher cognitive functions are very similar to humans. Members of the Working Party observed research being undertaken on macaque monkeys which sought to investigate how activity in groups of brain cells in the motor cortex controlled specific hand and finger movements. The purpose of this research was to increase understanding of how stroke can impair use of the human hand. Similar research has led to the development of treatment to reduce the symptoms of Parkinson's disease (see Box 5.4). With regard to welfare implications arising from the experimental procedure itself, the introduction of very fine microelectrodes into the brain is not painful for the animal, because the brain itself has no pain receptors.

***Animal development***

10.6 The study of animal development has contributed to our knowledge of basic processess in human embryonic development. Chick, zebrafish, rodent and frog embryos are often used to gain a better understanding of the roles of single genes or groups of genes in developmental processes (paragraph 5.12). GM mammalian embryos have also been created for this purpose (paragraph 5.13). Research on juvenile and adult animals has also been important, especially in mammals, where major development occurs after birth (paragraph 5.15).

***Genetic research***

10.7 Genetic studies constitute a significant part of animal research and are likely to increase dramatically in future, with experts in the field estimating that over the next two decades 300,000 new transgenic mouse lines could be created (paragraph 5.22). Spontaneous mutants, deliberate random mutations and targeted mutations have all provided useful information on gene function (paragraphs 5.16-5.22). Large programmes of mutagenesis in mice have been initiated, which aim to characterise the functions of both individual and combinations of mouse genes (see paragraph 7.5). With regard to the welfare of animals used in such research, the defects that may result from a genetic manipulation cannot usually be predicted in advance. In many cases gene knock-outs produce no obvious abnormality, although in others, they may lead to serious effects. Studies vary considerably in design and conduct and the likelihood of negative welfare effects including minor or severe discomfort and increases in mortality and susceptibility to disease varies accordingly (paragraph 4.57). Methods of producing GM animals also have the potential to be painful and distressing. In mice, this usually involves hormone injections, surgical embryo transfer (which may be undertaken without pain relief) or surgery to produce vasectomised males, tail biopsy or ear notching. Where possible, the use of pain relieving medicines can help to reduce the effects for the animals (see paragraphs 4.12 and 4.58). The methods used to produce GM animals are relatively inefficient (3-5%), and substantial numbers of animals do not have the desired genetic traits and are usually euthanised (see Box 5.6).

***Animal cloning***

10.8 The process of cloning animals, which aims to create genetically near-identical offspring (paragraph 5.26), has a range of potential uses. These include medical applications such as facilitating the provision of organs for xenotransplantation, or pharming (paragraph 5.31). In principle, the technology can also be used for other purposes, for example to produce 'copies' of farm or sport animals with desirable traits, or to replace deceased pets. The technology is still very inefficient and there is a high probability of malformations. The long-term implications for welfare are not yet known for most animals (see paragraphs 3.41–3.43).

***Production of research tools***

10.9 Animals are widely used for the production of antibodies, which can be employed to identify, localise, quantify or purify a substance. To produce antibodies against an antigen of interest, an animal is repeatedly immunised with the antigen together with an immunostimulant (an adjuvant), and the antibodies are then harvested from the blood. The use of adjuvants in animals (which are not always required) can lead to the development of sterile abscesses or lameness after intramuscular injections into the leg. Immunisation can sometimes cause anaphylaxis which can be lethal. The use of mice, primed with an irritant, to produce large amounts of a monoclonal antibody in ascitic fluid in the peritoneal cavity is now rarely used in the UK; it has been replaced by an *in vitro* method.

## Animals in the study of human disease (Chapter 6)

10.10 Animals are used for the study of diseases affecting animals and humans to learn about causal factors, development and infectivity, and to explore therapeutic and preventative strategies. Many diseases induce complex and dynamic interactions between molecular, cellular and organ systems. Although *in vitro* experiments form an important part of research on diseases, scientists whose work involves animals emphasise that their work is crucial in understanding the interactions of these complex processes. Disease models can be obtained by discovery of spontaneous mutations, by selective breeding or by means of more targeted interventions such as genetic modification (paragraphs 10.16-10.18). If animals are to provide useful models, it is only important that relevant elements of their bodily processes are similar to those of humans. In some cases this may mean that although animals can be useful models for the study of diseases that cause great suffering in humans, the animals used may not experience the same level of discomfort. In others, animals may spend much (or all) their lives suffering from the animal form of the disease under study.

10.11 We described two recently developed disease models for rheumatoid arthritis (RA) and transmissible spongiform encephalopathies (TSEs). RA is one of the most common human autoimmune diseases. It is a crippling disease resulting in chronic inflammation of the joints, the cause of which remains unknown. In the last ten years there have been major advances in the understanding of the disease process. Both animal and non-animal approaches to research have been pursued simultaneously and often by the same researchers (paragraph 6.5). Study of rodent models with induced arthritis helped to contribute to the discovery that an immune molecule called TNF plays a crucial role in the inflammatory process. The animals experienced a painful swelling of the paws, and damage to the cartilage which would have affected the animals' welfare since rodents use their front feet extensively for grooming, holding food, eating and moving around. Various interventions were tested on the models, aimed at neutralising the inflammatory reactions by blocking the molecule through administration of antibodies. This strategy had dramatic effects on reducing the inflammation and damage caused by the disease in mice. In the early 1990s, clinical trials were carried out in humans and proved successful (see paragraphs 6.9-6.10). Some 200,000 people have since been treated effectively with the antibody therapy.

10.12 When BSE emerged in cattle in the mid-1980s little was known about its causes and infectivity (paragraph 6.12). Experimental animals were used to test the novel hypothesis that the disease was caused by abnormal forms of a protein, called prions. Transmission of BSE to monkeys by injecting bovine prions into their brains was the first demonstration that the disease was able to cross the species barrier to primates, and ultimately also to humans. In 1996, the first cases of vCJD occurred in people in the UK who had been exposed to the BSE agent. Experiments using mice were used to define important stages in the development of spongiform encephalopathies. The mice typically experienced progressive

neurological dysfunction, behavioural and gait abnormalities as well as weight loss. Researchers aimed to limit suffering by euthanising animals when they were unable to eat or drink without assistance or when they reached certain stages that were known to precede the experimentally induced terminal disease.

10.13 The scientific research that was carried out on BSE strongly influenced public health policy and led to the introduction of control methods in cattle and sheep. Animal tests showed that pigs and chickens were not susceptible to BSE when fed with infected tissue, which meant that the same control measures were not necessary for these species. Other research helped to identify further measures to protect humans from infective TSE agents. These included the removal of brain and spinal cord material from meat destined for public consumption and the implementation of the Over Thirty Month Scheme (paragraph 6.22). BSE pathogenesis studies in sheep also showed that blood can be a source of infection. In response to the hypothesis that two people who died of vCJD had been infected by a blood transfusion, the Department of Health announced in 2004 that anyone who had received a blood transfusion in the UK since 1980 would no longer be able to donate blood (paragraph 6.24).

10.14 Animal disease models were also used for research on hepatitis C, and polio. The hepatitis C virus worldwide affects 170 million people, many of whom develop cirrhosis and liver cancer. Polio is estimated to be responsible for causing disability in more than half a million people around the world per year in the late 1950s and early 1960s. There are hopes that the virus will soon be eliminated. The hepatitis C virus was found to infect only primates and early research involved chimpanzees and monkeys. With regard to welfare implications, if the animals develop hepatitis C, they are likely to experience similar physiological symptoms to humans. These may range from malaise to paralysis. The symptoms associated with polio affect a whole range of behaviours including ambulation, climbing, social interactions, grooming and foraging. Affected animals are likely to be aware of their deficiencies and so may experience distress at not being able to carry out normal behaviours. In long-term research animals have to be isolated as they will be infectious to other animals and humans, and their welfare may be negatively affected.

10.15 We described two areas of research where progress continues to be difficult. Despite the use of animal research to improve understanding about the biological processes underlying diseases such as HIV/AIDS and various forms of cancers, fully effective cures or vaccines have not yet been developed. Due to the complex pathogenesis of these diseases which have many different sub-types in humans and animals there are inherent difficulties in studying them and developing successful animal models. However, effective treatment has been developed for some types of cancer, such as breast or prostate cancer. Scientists involved in this type of research believe that refined models (especially primate models) may accelerate scientific progress. Transgenic mice have also been developed which express human receptors on their cells and may be used as replacements for primates in certain experiments (paragraph 6.35).

## GM disease models (Chapter 7)

10.16 GM animals are increasingly being used in the study of human disease. Scientific advances allow the creation of animal models of diseases with a genetic component in a targeted way, reflecting the genetic patterns that underlie the human version of the disease. Examples include models for diabetes, deafness, psychiatric disorders, neurodegenerative disorders and cancers.

10.17 Some animals are used for the study of genetic diseases because of the strong genetic similarities between humans and many other species. For example, 99 percent of genes in

mice have direct counterparts in humans (paragraph 7.2). Most biomedical scientists maintain that the similarities between mice and humans are sufficient to make informative comparisons. Furthermore, the differences may be as instructive as the similarities when investigating the mechanistic basis of disease (paragraph 7.10). Scientists using animals in this field therefore maintain that careful analysis of mouse models can provide significant information on the function of genes in mammalian disease processes (paragraph 7.10). Other species with suitable genomes for comparative studies such as the zebrafish and the rat are being increasingly used (paragraphs 7.11-7.13).

10.18 Information from mouse models has enabled scientists to investigate the relationship between mutations and the nature and severity of the disease they cause. The glucokinase gene in diabetes is one such example. The use of the mouse model *shaker1* has also led to the discovery of a gene causing profound hearing loss in both mice and humans (see paragraph 7.9). Mouse models are also important for investigating how one disease can produce varying symptoms in different individuals. Indirect changes, for example in levels of a protein or a hormone, may prove to be more suitable therapeutic targets than the genes themselves, as in the case of patients with neurodegenerative disorders (see paragraph 7.9). The use of GM animals can entail a wide range of welfare implications, as the animals involved usually suffer from the disease being studied for the duration of their lives (paragraph 4.57). They are also likely to be the subject of procedures carried out to characterise the different stages of the disease, including blood, metabolic and behavioural tests. The very low success rates in producing a strain of animal that can serve as a disease model also require attention (see Box 5.6).

## Animal use by the pharmaceutical industry (Chapter 8)

10.19 Use of animals within the pharmaceutical industry is a crucial part of the research and development process for new medicines. The number of animals used by the pharmaceutical industry has fallen over the last two decades due to the application of new technologies, new materials and increased use of computational analysis (see paragraph 8.4). In the UK in 2003, 36 percent of the total number of procedures performed on animals were undertaken by the commercial sector.

10.20 Relatively small numbers of animals are used in the early stages of drug discovery, particularly in the identification of targets for possible medicines. Many of the animals used at this stage are GM mice. They are used to ascertain whether, for example, specific receptors might respond to chemical compounds which can be developed into new medicines. Animal models that reproduce relevant aspects of human genetic conditions, such as sickle cell anaemia, can be used to test how people affected by the disorder may react to different chemical compounds (see paragraph 8.16).

10.21 Sixty to eighty percent of animals used by the pharmaceutical industry are involved in the process of characterising promising candidate medicines (Table 8.1). Rodents are most commonly used, but larger animals, including rabbits, dogs and primates, are also used (see paragraph 10.24). Before a potential medicine is tested in human trials, the regulatory authorities must ensure that it has an acceptable balance of safety and efficacy, usually requiring data obtained from animal tests. Twenty five percent of the total number of procedures using animals in 2002 in the UK were conducted for the purpose of 'applied human medicine'. Once a medicine is in clinical trials, animal tests continue to be carried out (paragraphs 8.27 and 8.29).

10.22 For certain biological compounds such as vaccines, animal testing is required for each batch that is produced, to ensure potency and safety (see paragraphs 8.35-8.36). Depending on the type of test there can be serious welfare implications. For example, if death is the

required endpoint, or if it is the easiest endpoint to observe reliably, it may be used. In specific cases, the terminal stages of a lethal endpoint may not involve much, if any, suffering as the animal may be comatose. However, the suffering that may have taken place beforehand can be substantial and may involve considerable distress including loss of appetite, malaise, convulsions or imbalance rather than pain.

## Animal use in toxicity testing (Chapter 9)

10.23 Tests involving animals play an important role in the safety assessment of compounds such as medicines, household chemicals, agrochemicals and industrial chemicals when brought into contact with humans, animals or the environment. Chemicals are assessed for their potential to cause irritation, physiological reactions, cancers, developmental complications for foetuses *in utero*, and effects on fertility. Sixteen percent of the total number of procedures using animals in 2003 in the UK were conducted for the purpose of 'toxicology or safety evaluation'. Specified doses and exposures of the chemicals are given to animals, from which information regarding safe human dose and exposure levels is then extrapolated.

10.24 Rats and mice are most commonly used in toxicology (74 percent of procedures). Other tests involve non-rodent species such as fish, rabbits, chickens, dogs and primates. Tests range from one single high dose to long-term exposure to a particular chemical, in order to observe the effects seen when a product is used (or misused) in different situations. The tests are designed to mimic the possible routes of exposure that humans might be subjected to, such as through the mouth, skin, eyes or airways. The information produced is used mainly to ascribe chemicals to bands of acute toxic effects, which restricts how they may be used. Regulatory requirements demand that the studies are conducted in a way that minimises the numbers of animals used and which reduces pain and distress as far as possible (paragraphs 9.4 and 13.17).

10.25 Toxicity testing has a range of welfare implications for test animals, some of which can be severe. These effects are minimised by the 'build-up' approach in which severe reactions can be detected at an early stage (acute toxicity followed by chronic toxicity, paragraph 9.14). More recently alternative methods have been developed which, when utilised during the early stages of testing, may prevent very toxic substances from being administered to animals. For example, studies that evaluate irritant potential to the skin or eye are preceded by tests that use *in vitro* human or animal tissue to identify chemicals with the potential to cause severe irritation or corrosion. These tests are termed 'non-animal pre-screens'. However, it is an intrinsic part of most toxicity tests to cause some form of harm to animals.

10.26 A full complement of toxicity tests can entail the use of between 1,500 and 3,000 animals, although not all of these will suffer the most harmful consequences of the testing. The adverse effects range from minor changes such as reduced weight gain to severe effects including loss of organ function, leading to death (paragraphs 9.32-9.37). Certain methods of reduction and refinement are relevant to toxicology, but progress has been difficult (paragraphs 9.3-9.4).

## Extrapolating the results of animal studies to humans: the scientific validity of animal research

### *General arguments about scientific validity*

10.27 Some of those who oppose animal research on scientific grounds argue that anatomical, physiological, cellular, biochemical and other differences between humans and animals seriously compromise most extrapolations of results from animal studies to humans.[1] A few take an absolutist position. They claim that the differences between humans and animals are so substantial as to make any such extrapolation scientifically meaningless, and that the only sufficiently reliable model with which to study humans are humans. Others argue that clinical observations in humans often reveal medical discoveries, which are then subsequently 'validated' in animals (see paragraph 2.4). The conclusions drawn from such a position are that (i) most animal research has proved to be dangerous and misleading and (ii) the use of animals should be abandoned and replaced by other methods such as cell and tissue culture, computer-simulation research, computer-simulation research, or post-mortem research. There are frequent claims that these approaches are more reliable, especially if they use human-based models or data. Some of these views were illustrated by the following responses to the Consultation:[2]

> 'The only reliable model for a human is a human.'
> *Anonymous*

> 'It is not proved that animal research is a superior route to information. Transference of results can, and has, proved misleading.'
> *International Primate Protection League UK*

> '…if, as we maintain, animal experiments do not advance human medicine, there is no issue other than the fact that conducting animal experiments is absurd, is unethical for both animals and people and should cease immediately.'
> *Europeans for Medical Advancement*

10.28 Other opponents of animal research do not take such an absolutist stance, believing that, in at least some cases, animals can be used as scientifically useful models for humans, although they may remain critical of any animal experiment on ethical grounds. Like those who adopt an absolutist position, these opponents also tend to argue that non-animal approaches yield results that are more relevant for humans. They assert that greater efforts should be made to develop and implement non-animal approaches as replacements for animal studies.[3] Whatever their position in the spectrum, all opponents are also likely to assert that researchers over-state the predictive value of animal experiments.[4]

10.29 Those questioning the scientific validity of animal research employ a range of examples to support their general arguments.[5] These include:

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1 The arguments are usually framed in terms of extrapolation from animal studies to humans. In principle, the same arguments could be applied to extrapolations between different animal species, for example in veterinary research when mice are used as 'models' for pigs or horses. While some of the discussion in this section will relate to both claims, in general we focus on issues concerning the transferability of data from animals to humans.

2 See, for example, Greek CR and Greek JS (2002) *Specious Science: How genetics and evolution reveal why medical research on animals harms humans* (New York: Continuum Publishing).

3 See Chapter 11 for a discussion on the scope and limitations of the Replacement approach.

4 See, for example, LaFollette H and Shanks N (1996) *Brute Science: Dilemmas of animal experimentation* (London: Routledge).

5 For further discussion, see Animal Procedures Committee (2003) *Review of Cost-Benefit Assessment in the use of Animals in Research* (London: Home Office), pp17-34.

i) specific cases in which it is claimed that animal models have failed to predict effects in humans and/or in which research using animals has not led to clinical benefits;[6]

ii) more-general examples of areas of research in which it is argued that preventative medicine and public health measures have made a greater contribution to improvements in human health than vaccines, treatments or other interventions whose development involved the use of animals;[7]

iii) cases in which it is claimed that animal experiments have not benefited human health because the objectives were not original, not relevant, not current or not worthwhile, or because the experimental design was poor.[8]

10.30 Most of those who argue that animals can provide scientifically valid 'models' for humans do not contend that every use of animals yields immediately useful results, nor that the use of animals is always the most suitable approach. But they firmly refute the claim that cases in which animal experiments can be regarded as flawed are sufficiently widespread and indicative of a common, underlying difficulty such that the concept of animal research as a whole is flawed. The examples given in Chapters 4–9 support this view.

10.31 We have examined arguments about the implications of the evolutionary relatedness of humans with other animals (see Chapter 4). We concluded that continuities in the form of behavioural, anatomical, physiological, neurological, biochemical and pharmacological similarities provide sufficient grounds for the hypothesis that animals can be useful models to study specific aspects of biological processes in humans, and to examine the effects of therapeutic and other interventions (paragraphs 4.8-4.10). We described a wide spectrum of different kinds of biomedical research activity, between them employing a variety of different kinds of animal model to address a range of different objectives. They included basic physiological studies (Chapter 5), more applied work on human diseases and genetic disorders (Chapters 6 and 7), pharmaceutical discovery and development (Chapter 8), and toxicity testing (Chapter 9). The examples showed that research and testing involving both genetically normal and GM animals has proved relevant to humans and, in combination with other methods such as *in vitro* and clinical studies, has contributed significantly to biomedical understanding. The cases presented show that there are numerous instances in which extrapolations from animal studies can be made in a meaningful way, provided that the animals involved are sufficiently similar to humans in relevant aspects of the biological phenomenon or disease being studied.

10.32 The examples in Chapters 5–9 also illustrated some of the difficulties involved in extrapolating from animals to humans. Although there has been extensive use of animals in HIV/AIDS research, modelling of this complex disease is difficult, and all of the currently available animal models have limitations. In some cases, promising vaccines have been used successfully in

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6 A variety of such examples are presented in: Greek and Greek (2002) *Specious Science: How genetics and evolution reveal why medical research on animals harms humans* (New York: Continuum Publishing); and LaFollette and Shanks (1996) *Brute Science: Dilemmas of animal experimentation* (London: Routledge).

7 For example, it has been observed that major reductions in incidence of many common infectious diseases coinicided with the introduction of clean water and good sanitation in the last century in Europe, before effective vaccination was available. Another example argument is the possibility of preventing cancers through environmental and/or life-style changes, which could remove the need for curative approaches. Animal Procedures Committee (2003) *Review of the cost-benefit assessment in the use of animals in research* (London: HO), p24.

8 Animal Procedures Committee (2003) *Review of the cost-benefit assessment in the use of animals in research* (London: Home Office), p25; For example, the NAVS have cited an experiment performed on ferrets to test the effects of a bacterial toxin. The bacteria used in this study are a well known cause of food poisoning in humans. The NAVS claim that the data was already available from human studies, and previous animal studies NAVS (2001) *Response from the National Anti-Vivisection Society to the Animals Procedures Committee consultation paper on the cost-benefit assessment*, p29 available at: http://www.navs.org.uk/download_files/news/Benefit_Assess.pdf Accessed on: 5 May 2005;

macaques, but have not provided protection for humans. Fundamental differences between the HIV/AIDS disease processes in the macaque model and in humans need to be considered carefully in making predictions from one to the other (paragraphs 6.36–6.37).

***All modelling approaches face limitations concerning transferability and predictability***

10.33 Given the vast complexity and variability of biological systems, it is not surprising that there are sometimes problems in developing effective experimental approaches in biomedical research and in extrapolating from model systems to humans (see paragraph 8.37–8.40). The difficulties, however, are an intrinsic part of any modelling approach that relies on surrogates for the range of organisms of interest. Nor are they confined to animal studies, but are also encountered in developing and applying other experimental approaches, such as *in vitro* and clinical studies. None of these methods can reproduce exhaustively all the features that characterise the wide diversity and variation of genetic and biological processes that occur in a population of humans, as is clear from the following examples:

i) **Limitations of *in vitro* research:** differences between human cells *in vitro* and *in vivo* can pose challenges in extrapolating findings from research on the functioning of human cells in culture to the functioning of human cells *in vivo* (see Chapter 11 for further discussion).[9] Yet more acute challenges arise in using the findings from cell culture studies to make predictions relating to the integrated physiology of intact tissues, organs or the whole human body.

ii) **Limitations of human clinical trials:** even if the animal-research stage was omitted from the development of new medicines, intrinsic problems resulting from the way clinical trials are conducted remain. First, human clinical trials typically involve testing a drug on 1,000–5,000 human volunteers and patients. If a side effect occurs in 1 in 10,000 patients, it is likely to become apparent only after the product is marketed (see Boxes 8.6 and 8.7). Secondly, human trials usually involve a relatively homogeneous sample of patients in order to distinguish clearly between the effects of the therapy (the 'signal') against the background of variation between different patient' responses (the 'noise').[10] Such trials, moreover, frequently provide little, if any, information about the effects of drug interactions, since they usually do not mimic the actual situation in which patients may take several different medicines at the same time.[11] Uncertainties about the effects of treatments in the clinical setting are therefore inevitable,[12] and clinicians must exercise judgement in extrapolating the results of clinical trials to individual patients (see paragraph 11.21).[13]

9 This point draws on Horrobin's provocative discussion in a recent opinion: Horrobin DF (2003) Modern biomedical research: an internally self-consistent universe with little contact with medical reality? *Nat Rev Drug Disc* **2**: 151–4.

10 Fletcher RH (2002) Evaluation of interventions *J Clin Epidemiol* **55**: 1183–90.

11 Stricker BHCh and Psaty BM (2004) Education and debate article: detection, verification and quantification of adverse drug reactions *BMJ* **329**: 44–7.

12 Chalmers I (2004) Editorial: Well informed uncertainties about the effects of treatments: how should clinicians and patients respond? *BMJ* **328**: 475–6.

13 Fletcher RH (2002) Evaluation of interventions *J Clin Epidemiol* **55**: 1183–90.

**Box 10.1 : Toxicity studies in humans: number of trial participants required to be 95 % certain* of detecting cases of adverse events directly related to the medicine under study**

| Incidence | 1 case | 2 cases | 3 cases |
|---|---|---|---|
| 1 in 100 | 300 | 480 | 650 |
| 1 in 200 | 600 | 980 | 1,300 |
| 1 in 1,000 | 3,000 | 4,800 | 6,500 |
| 1 in 2,000 | 6,000 | 9,600 | 13,000 |
| 1 in 10,000 | 30,000 | 48,000 | 65,000 |

* A confidence limit of 95% (P<0.05) is generally agreed to be an acceptable level of certainty for trial data. Thus, 300 people would be needed to ensure 95% confidence to identify one person who will experience adverse reactions for which the average incidence is 1 in 100. (100, or 200 trial participants would give far lower levels of certainty). Higher levels of certainty are possible, but require disproportionately higher numbers of trial participants. As the table shows, higher numbers are also required to identify adverse events that occur less frequently. The closer the number of trial participants is to the number of people who will eventually use the medicine being assessed, the higher the levels of certainty. Complete certainty is, for statistical and practical reasons, impossible to achieve. See also: Stark NJ (2000) *Clinical Trials Design, Third Edition*, Clinical Device Group Inc, Chicago, IL; Friedman LM, Furberg CD and DeMets DL (1999) *Fundamentals of Clinical Trials* (Springer); Kirby A, Gebski V and Keech AC (2002), Determining the sample size in a clinical trial, available at: http://www.mja.com.au/public/issues/177_05_020902/kir10425_fm.html. Accessed on: 3 May 2005.

10.34 These observations help to explain why adverse reactions sometimes occur in humans when medicines are brought to the market after testing *in vitro*, in animal studies and in human clinical trials, none of which individually, or collectively, have allowed the prediction of these effects. Nevertheless, such adverse reactions generally occur in relatively few patients, and only a small fraction of marketed medicines have been withdrawn for safety reasons (Boxes 8.6 and 8.7).

10.35 To what precise degree animals can be said to be useful models of human disease continues to be controversial. Taking into account evidence presented in Chapters 5–9 and the above discussion, we note that there have been a great number of cases where animals have been used successfully to provide models for humans (or other animals of different species) We therefore agree with the finding of a recent Report by the Animal Procedures Committee (APC), which observed that:

> 'the scientific validity of animal experiments is a condition capable of being fulfilled, but has to be judged case by case and subjected to detailed critical evaluation'.[14]

10.36 We draw a similar conclusion with regard to the assertions that animal experiments lack internal validity because they sometimes fail as a result of poor experimental design or other methodological problems. While it is clear that such examples exist (see paragraphs 6.32, 6.37 and Box 8.4), they are insufficient to support the claim of a general flaw. Rather, those advocating the use of animals in research take the view that these cases point to a need to carry out a critical evaluation of any design of a study, regardless of the method or subject employed (be it computer studies, *in vitro*, animal or human).[15] With regard to the special case of thalidomide, critical reflection helped prompt the introduction of regulations that require more rigorous and consistent testing of medicines in animals in order to help prevent further tragedy (Box 8.4).

14 Animal Procedures Committee (2003) Review of the cost-benefit assessment in the use of animals in research (London: HO), p26

15 see Chapter 6, footnote 40.

***Critical evaluation of scientific validity***

10.37 We have observed that, in principle, animal studies can be scientifically valid. Nevertheless, there is a need for continuing review of the scientific case for using animals in research and testing. It is axiomatic that any such use should be accompanied by active and critical reflection on the validity and relevance of the models and research studies.[16] Although scientific claims in favour of the validity of animal research are not usually made in absolute terms, some public statements can over-generalise and tend towards the absolute.[17] It is important, for a number of reasons, not to overstate the predictive value and transferability of animal research to humans, because:

- Critical reflections are a vital part of good scientific practice, having value in determining directions and priorities for future research, as well as in interpreting the results of particular studies and refining models.
- Better understanding of the differences between animal models and the human organism can in itself be instructive and can prompt beneficial lines of research (paragraph 7.10).
- It is possible that lack of critical evaluation of the validity of animal models can on occasion be misleading (paragraph 6.32).
- Over-emphasising the predictive value of animal tests can make acceptance of alternative approaches unnecessarily difficult. In toxicity testing, for example, existing animal methods have been validated by the OECD 'by experience' and have not been subject to the same formal validation processes as those now required for new non-animal Replacements (see paragraphs 9.4 and 11.24). 'Claiming too much' for the predictive value of existing animal methods can sometimes put unnecessary barriers in the way of regulatory acceptance of new *in vitro* methods.[18]

10.38 It is clear that continuing critical evaluation of the scientific validity of animal models makes good scientific sense, and as our description in Chapters 5–9 shows, is usually a part of good scientific practice. For example, the majority of the scientific community takes the view that similarities between mouse and human genomes are sufficient to permit informative comparisons between GM mouse models of human diseases and the human clinical conditions in specific cases. Nevertheless, such models require careful analysis in order to assess their relevance and effects (see Box 10.2).

16 This argument also applies to the use of animals in studies that are extrapolated to other animal species.

17 See Animal Procedures Committee (2003) Review of the cost-benefit assessment in the use of animals in research (London: HO) for further discussion.

18 Some commentators claim that it is easier to achieve OECD approval for new animal, as compared to non-animal methods, see: Written evidence submitted by Dr Gill Langley to the House of Lords Select Committee, page 100 based on references from the OECD.

### Box 10.2: A recent retrospective study of the potential value of knock-out mouse models* in pharmaceutical discovery and development

The study aimed to address 'common and varied…questions concerning the value of mouse genetics for drug discovery', including the following.

- What is the correlation between mouse and human physiology and hence the relevance of knock-out models in developing small-molecule drugs?
- Does gene compensation (when the expression of another gene alters to compensate for the loss of another during development) prevent identification of the true function of the genes that have been knocked out?
- Since current technology means that the genes are usually knocked out very early in development, in what sense are the effects of the lack of a particular gene throughout development relevant to the function of the gene in adult animals?
- How far is the embryonic or neonatal death of some knock-out mouse lines likely to prevent the identification of many of the best drug targets in future?

In light of such questions, the study demonstrated that the 100 best-selling human pharmaceutical medicines between them have 43 human biochemical targets, the genes for 34 of which have now been knocked out in mice. A literature review revealed that, of these 34 knock-out models, 29 (85 percent) provide a direct correlation with the therapeutic effect of the relevant medicine. In the remaining five cases, early (e.g. embryonic or neonatal) lethality or unrelated abnormalities meant that the knock-out mice were not useful models for humans.†

It might be argued that such a finding is not surprising since the knock-out mice were generated after the medicines were developed, when the mechanism of action of the medicines was already known. However, the authors also assert that more 'prospective' use of knock-out mouse models is currently yielding benefits. A number of new pharmaceuticals are being developed against human biochemical targets the function of which has been determined using genetic research involving mice, including treatments for osteoporosis and obesity.‡

* That is, mice in which one or a few genes have been deleted, or otherwise disrupted, so as to prevent their expression.

† Zambrowicz B and Sands A (2003) Knockouts model the 100 best-selling drugs – will they model the next 100? *Nat Rev Drug Disc* **2**: 38–51.

‡ Zambrowicz B and Sands A (2003) Knockouts model the 100 best-selling drugs – will they model the next 100? *Nat Rev Drug Disc* **2**: 38–51.

10.39 The study described in Box 10.2 is an example of a systematic attempt to evaluate the scientific validity of using animals as models for humans, by directly comparing findings in animals with the results of corresponding clinical studies. There have also been two recent meta-analyses of such systematic reviews. One was conducted 'to find out how animal research had informed ensuing clinical research',[19] the other to assess the value of pre-clinical animal studies in permitting safe and effective first-dose studies of potential new medicines in humans.[20]

10.40 The first paper, by Pound *et al*. (2004), examined six reviews, each of which compared animal and clinical findings in a specific and problematic therapeutic area (heart disease, stroke, wound healing). The authors concluded that these six reviews provide little evidence to support the view that animal research has contributed to the treatment of human disease. The study has been used to support claims that there is 'no-evidence base for animal research'.[21] But it has also been strongly criticised, in particular for its selectivity, given that other systematic reviews were identified by the team but were excluded from the analysis. Of the six reviews discussed in the paper, five were initiated following lack of success in clinical trials, which could have been predicted from better analysis of the relevant animal studies. The sixth was initiated because of difficulties in establishing an animal model of the relationship between social status and coronary heart disease. Nevertheless, the study has served to highlight cases in which there were some methodological problems in the animal studies and/or in which full analysis of the animal results available would have predicted the ineffectiveness of the treatment, had such an analysis been done before clinical work started.[22]

19 Pound P, Ebrahim S, Sandercock P *et al*. (2004) Where is the evidence that animal research benefits humans? *BMJ* **328**: 514–7.

20 Greaves P, Williams A and Eve M (2004) First dose of potential new medicines to humans: how animals can help *Nat Rev Drug Disc* **3**: 226–36.

21 See, for example, rapid response letters to the *British Medical Journal*.

22 See for example Blakemore C and Peatfield T (2004) Missing evidence that animal research benefits humans *BMJ* **328**: 1017-8

10.41 The second meta-analysis draws on the work of Olsen *et al*.,[23] among others, and concluded that, although the relevant available data are 'fragmentary',[24] the concordance between short-term toxic effects of new pharmaceuticals in animals and humans (during clinical trials) was 71 percent. This means that 71 percent of human acute toxicities resulting from compounds that entered clinical trials were predicted by pre-clinical safety pharmacology or toxicity studies in animals. It is noteworthy that this conclusion has been used as part of cases both 'for' and 'against' the predictive value of pre-clinical animal studies: thus while 70 percent of human toxicities were predicted, 30 percent were not, and the rodent tests alone predicted only 43 percent of human toxicities.[25]

10.42 It is also worth noting that the toxic events considered by Olsen *et al*. are likely to be at the more minor end of the spectrum of potential adverse effects. Compounds causing significant damage to animals would not have entered clinical trials. Reliable systematic data on compounds eliminated before human dosing because of major organ toxicity in animals are not available. It is therefore not possible to judge how many compounds were rejected because of their adverse effects in animals.[26] As before, this observation could be used to support or contest the scientific validity of animal tests. On the one hand, it can be argued that actual concordance is *greater* than 70 percent, when the animal tests showing adverse effects too significant to proceed to human trials are taken into account. On the other, it might be argued that animal research may lead to the loss of potentially useful medicines for humans as compounds might be removed in the screening process because of significant toxicity in animals which would perhaps not occur in humans. However, those defending the use of animals would argue that the option of 'losing' some compounds in this way can be viewed as preferable to exposing humans to medicines that have not undergone prior testing.

10.43 Finally, it should be noted that the Olson study only considered toxic events observed in human clinical trials, i.e. short-term effects. Longer-term toxicities such as carcinogenicity and teratogenicity were not assessed. For these long-term toxicities it has been difficult to establish the validity of animal tests[27] which have been criticised by toxicologists.[28] Thus the concordance between animal and human long-term toxicities, if it could have been measured, may prove lower than found by Olson *et al*. for short-term toxicities. At the same time it needs to be acknowledged that assessment of long-term toxicity is a highly complex process. For example, while it may be straightforward to identify a number of people who have taken a certain medicine at some point in the past, it may be less straightforward to correlate possible negative states of health which occur, for example, a decade after the medicine has been used. Since people may have taken a range of other medicines in the meantime, and since factors such as lifestyle or exposure to chemicals in the workplace may also play a role, many factors need to be considered.

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23 Olson H Betton G, Robinson D *et al*. (2000) Concordance of the toxicity of pharmaceuticals in humans and in animals *Regulat Toxicol Pharmacol* **32**: 56–67.

24 The authors note that much of the relevant information is held by government regulatory authorities and pharmaceutical companies and is not publicly available in the peer-reviewed scientific literature. The authors state that they can 'only learn from experience and then only if we have access to information'.

25 Animal Procedures Committee (2003) *Review of the cost-benefit assessment in the use of animals in research* (London: HO).

26 Greaves P, Williams A and Eve M (2004) First dose of potential new medicines to humans: how animals can help. *Nat Rev Drug Disc* **3**: 226–36.

27 Lo WY and Friedman JM (2002). Teratogenicity of recently introduced medications in human pregnancy. *Obstet Gynecol* **100**: 465-73.

28 For example, Ennever FK and Lave LB (2003). Implications of the lack of accuracy of the lifetime rodent bioassay for predicting human carcinogenicity. *Reg Toxicol Pharmacol* **38**:52-57; Johnson FM (2003) How many high production chemicals are rodent carcinogens? Why should we care? What do we need to do about it? *Mutat Res* **543**:201-15; and Gottman E, Kramer S, Pfahringer B *et al.* (2001) Data quality in predictive toxicology: reproducibility of rodent carcinogenicity experiments *Environ Health Perspect* **109**:509-14; Kennedy DL, Uhl K and Kweder SL (2004) Pregnancy exposure registries *Drug Saf* **27**:215-28.

## Summary

10.44 The first part of this chapter summarised the findings of our description of the range of scientific uses of animals in research. Across and within each area the benefits take a wide range of forms. Research is undertaken to understand animal behaviour, and basic biological processes; to understand the mechanisms of diseases affecting humans and animals in order to develop effective preventative and therapeutic interventions, and to test the safety of compounds for humans, animals and the environment. Some of the research findings have immediate and directly applicable results, whereas others contribute primarily to the scientific body of knowledge.

10.45 The welfare implications for animals used in research are as varied as the benefits. In appropriately conducted purely observational research of animals in their natural habitat there are no negative effects at all. Whether or not animals used in laboratories experience pain, suffering or distress depends on a range of different aspects: of the animal's environment. In all kinds of laboratory-based research there are contingent factors, arising from the conditions of transport, breeding, housing, and handling. Then there may be effects associated with procedures connected directly to specific elements of the experimental design. For example, the taking of a blood sample is a typical procedure that is applied to many research animals. Animals that are used as disease models are likely to experience the symptoms typical for the disease. Whether or not animals experience pain, suffering and distress associated with experimental procedures is highly variable and depends on standards of handling and husbandry and whether or not the experiment permits the use of pain relieving medicines and anaesthetics.

10.46 The second part of this chapter addressed issues relating to transferability of results obtained from animal research to humans. Drawing on discussion in Chapters 5–9 we concluded that animal research has been, and can potentially be, scientifically valid, in that it is possible to extrapolate from animal models to humans (or other animals) in specific cases. Each type of research has to be judged on its own merits and must be subject to critical evaluation. Although we have not undertaken an extensive review of the literature, it appears that there is a relative scarcity of systematic reviews and meta-reviews that address the question of the scientific validity of animal experiments. Care needs to be taken in interpreting their findings. One analysis which has received considerable attention appeared to ‘over-sample’ the difficulties, examining primarily scientific areas in which the development and use of animal models has proved problematic. By contrast, areas in which extrapolations have proved relatively straightforward seem to attract little or no comment about the predictive value of the animal studies, as the results are simply reported and used. Stemming partly from this difficulty, we are aware that data emanating from reviews of the validity of animal experiments have been interpreted and used in different ways by both opponents and proponents of the scientific validity of using animals.

# Section 3

## Alternatives

# Chapter 11

## Replacements

# Replacements

## Introduction

11.1 Replacing, as far as possible, the use of animals for experimental purposes is a highly desirable goal. Progress in reducing animal use, partly but not wholly through developing Replacements, has been made in the UK. Nevertheless over 2.7 million animals were still being used in experiments in 2003. In this chapter we explore the prospects for the Replacement approach. We begin by clarifying the use of the concepts of alternatives and Replacements. We then discuss several different notions within the concept of Replacement and differentiate between different forms (complete and incomplete). We consider the role of non-animal methods as 'advanced' methods, as adjuncts to animal experiments, and as a way of avoiding animal use altogether. We then turn to the potential for Replacement of animals in different areas of research, focusing on toxicity testing required by regulation, and basic research. We describe scientific and non-scientific barriers to further implementation of the approach, and comment on recent initiatives to overcome these. Replacement is only one of the Three Rs. Refinement, Reduction and Replacement are interrelated, and adjusting one can affect one or both of the others. We discuss Reduction and Refinement in Chapter 12.

## The current debate

11.2 There is much debate about the potential to replace animals in experiments with alternative methods. Some, often those involved in animal research, point out that the use of alternatives to animals is a legal requirement in the UK; that alternatives are always used if they are available; and that it is simply not possible to avoid the use of animals in most of the experiments that are currently carried out. They argue that large sums of money are spent on the search for alternatives; and that most research on Replacement methods is in fact undertaken by the scientific community.

11.3 Others, often those who work for animal protection organisations, and some scientists, argue that efforts to develop new, alternative methods and use of those already available could be increased substantially; that funding to develop (and validate) alternatives ought to be augmented; and that the search for alternatives requires greater commitment and focus. They argue that much more could be done with political will, greater resources and greater motivation within the scientific community. Some commentators also assert that animal experiments are poorly validated and sometimes misleading, and that alternative methods are therefore 'better science'.[1] The divergence of views on the role of alternatives is also illustrated by the following observations made by respondents to the Consultation:

> 'Far from being a separate activity, research into alternatives happens continuously when researchers seek and introduce new methods as part of normal working practice, and through the application of existing technologies. Replacement of animal use happens when information derived from new technologies allows us to gain knowledge which might otherwise have required animals. However, it is often unclear whether developments in say tissue culture are genuinely "alternatives" to animal use… They may simply be "different" methods which provide different information.'
> *AMRC*

[1] See, for example, Greek CR and Greek JS (2000) *Sacred Cows and Golden Geese* (New York: Continuum). See also New England Anti-Vivisection Society (2004) *Better Science: alternatives to animal research*, available at: http://www.neavs.org/betterscience/Alt-Contents.htm. Accessed on: 6 May 2005.

'Many of the suggestions for alternatives are based on misunderstanding or wilful misreporting of the facts. …the majority of medical research is nowadays on long-term degenerative diseases…, it is very difficult to see how any grossly simplified system (*in vitro*, *in silico*, etc.) can provide anything other than grossly simplified and misleading data.'
*Dr Chris Jackson*

'Despite British and EU legislation prohibiting the use of animals where a valid alternative exists, there are no centralised, comprehensible and easily accessible sources of information on alternatives for scientists to consult…. The establishment of a national centre of excellence for alternatives that could develop, promote and disseminate information and advice on alternatives to animals could solve this problem.'
*The Dr Hadwen Trust for Humane Research*

'The sooner the enormous sums of money that fund irrelevant experimentation on animals [are] diverted to relevant human-based, non-invasive methodologies, the sooner the pace of human medical progress will quicken.'
*Derek S. Paton, Dundee Animal Rights*

11.4 Arguments from both 'sides' of the debate about the potential to replace animals with alternatives are often applied to animal experiments *in general*, which is not particularly helpful or constructive. Animal experiments are used to provide information to try and answer a very wide range of scientific questions. The potential for using alternatives depends on the nature of the specific scientific question being addressed and therefore has to be evaluated on a case by case basis rather than in general terms, if progress in replacing animals is to be made.

## Use of the concepts 'Alternatives' and 'Replacements'

11.5 Before we consider these different areas in more detail, we need to be clear what is meant by the term alternative in the context of animal experiments. To the general public, an alternative is likely to mean *an alternative method that does not involve using an animal*. This is the principle encompassed by UK and EU laws, which require that animal experiments can only be carried out if the purpose of the programme of work '…cannot be achieved satisfactorily by any other reasonably practical method not entailing the use of protected animals.'[2] However, in recent years, the term 'Alternative' has been applied to all of the Three Rs as an overarching term referring to any procedure that reduces the harms caused to animals in experiments, not only by replacing them (Replacement), but also by reducing the numbers used (Reduction) or by causing less animal suffering (Refinement). Such a conceptual muddle is unhelpful and in this chapter we focus exclusively *on Replacements* since this is the area in which there is most debate about the potential to improve on current practice.

### *Definition and scope of Replacements*

11.6 Animal experiments are carried out to try to answer scientific questions. The term 'Replacement' is used to encompass methods that permit a given scientific purpose to be achieved without conducting experiments or other scientific procedures on living animals.[3]

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2 See Home Office (2000) *Guidance on the Operation of the A(SP)A 1986* (London: TSO), Chapter 5. Note that animals here means the animals covered by the Act and therefore only vertebrates, and one species of octopus; see Section 5.5 (a) of the A(SP)A, Article 7.2 of Directive 86/609.

3 Balls M (1994) Replacement of animal procedures: alternatives in research, education and testing *Lab Anim* **28**: 193–211; Balls M (2002) Future improvements: replacement *in vitro* methods *ILAR J* **43**, Supplement: 569–73; Gad SC (2000) Alternatives to *in vivo* studies in toxicology, in *General and Applied Toxicology*, Vol. 1, 2nd ed, Ballantyne B, Marrs TC and Syversen T (Editors) (London: Nature), pp401–24.

For *complete* replacement of animals, an alternative method should not require any animal-derived biological material. Examples of such methods or approaches include the use of predictions based on the physical and chemical properties of molecules, mathematical and computer studies of biological processes, analysis of epidemiological data, research involving human participants or research on isolated human cells and tissues in culture (see Box 11.1). However, many methods considered as Replacements also use some biological material obtained from living or humanely killed animals. These include research on cells and tissues derived from living or humanely killed animals for culture *in vitro* and animal-derived growth supplements such as serum derived from fetal or newborn calves. These methods can be called *incomplete* Replacements.[4]

### Box 11.1: Complete and incomplete replacements

***Computer studies and in vitro methods***

Mathematical and computer modelling studies (*in silico* techniques) comprise a variety of approaches. They include the prediction of the biological activity of substances, and the modelling of biochemical, physiological, pharmacological, toxicological and behavioural systems and processes.* *In vitro* techniques are also varied, increasing in complexity from subcellular (cell-free) fractions, through primary cells and cell lines grown in liquid suspension, and three-dimensional cultures, to tissue slices or fragments and even whole perfused organs, all consisting of cells or tissues derived from animals or humans.† Examples of techniques that involve cells, tissues or organs from animals that have been killed humanely include: the use of guinea pig skin to provide information that would previously have been obtained from tests on the skin of living animals, or the use of primary cell cultures to replace neonatal mice as a virus isolation or assay system.

***Human studies***

In many types of biomedical and toxicological research, animals are used because ethical considerations preclude conducting the experiments on humans. However, a number of approaches have been suggested which, in some cases, might replace the use of animals with studies on humans. These include non-invasive brain scanning to replace some experiments on primates,‡ and studies on ultra-low-dose ADME metabolism in human volunteers in the early stages of selection for potential medicines.∫ Human tissue samples can be used both for direct examination (e.g. histopathology) and in cell culture and other *in vitro* techniques.**

* Using, for example, molecular modelling and the development of quantitative structure-activity relationships; see Combes RD and Judson P (1995) The use of artificial intelligence systems for predicting toxicity *Pest Sci* **45**:179–94; Combes RD and Rodford R (2003) The use of expert systems for toxicity prediction – illustrated with reference to the DEREK program, in *Modelling Environmental Fate and Toxicity* Cronin M and Livingstone D (Editors) (London: Taylor & Francis); Assessing the cumulative effect of mutations: Kirkwood TB & Proctor CJ (2003) Somatic mutations and ageing *in silico Mech Ageing Dev* **124**:85–92.

† The European Collection of Cell Cultures (ECACC) operates a cell bank of peripheral lymphocytes from approximately 40,000 donors. Forty percent are in the form of lymphoblastoid cell lines representing around 450 genetic disorders. These lines are useful for the analysis of the role of genes in disorders that have a genetic component, for example cardiovascular diseases, Alzheimer's disease or depression.

‡ Langley G, Harding G, Hawkins P, *et al.* (2000) Volunteer studies replacing animal experiments in brain research *Alternat Lab Anim* **28**: 315–31.

∫ In this type of research, the absorption, distribution, metabolisation and excretion (ADME) of new medicines is assessed by measuring the effects of administering extremely low doses of candidate compounds. Extrapolations are then made concerning the effects of higher doses. The approach is at the early stages of development and is not yet suited to replace the use of animals in pharmaceutical research. Combes RD, Berridge T, Connelly J *et al.* (2003) Early microdose drug studies in human volunteers can minimise animal testing. Proceedings of a workshop organised by volunteers in research and testing *Eur J Pharm Sci* **19**: 1–11.

** Access to patients and issues of consent are critical factors in the feasibility of human studies, see paragraph 11.26.

11.7 Tests using invertebrates, or early developmental stages of vertebrates (i.e. before they reach the point at which their use in experiments and other scientific procedures is regulated), are also sometimes described as Replacements, even though they do not replace animals *per se*. For example, the horseshoe crab (*Limulus*) can be used to replace

[4] Although this practice does not replace the use of animals *per se,* it replaces the carrying out of procedures on living animals. Sacrificing the life of one animal can save the lives of many other animals, as its organs and tissues can be used in many different experiments. The humane killing of an animal carried out according to methods prescribed in Schedule 1 of the A(SP)A is not counted as a procedure.

the pyrogen test for microbial contamination of biological fluids, which was previously carried out in rabbits.[5]

11.8 The term Replacement can be misleading in that it implies that an animal technique is already in place, and that a non-animal technique can directly and completely replace it. Sometimes, non animal methods may directly replace an established animal test, but they are often simply the best or only method of addressing certain scientific problems, and are used within multi-disciplinary research programmes to reduce overall reliance on animal experiments. In other words they may *displace* or *avoid*, rather than *replace* animal experiments. We take the view that the concept of Replacement is best understood in a broad sense.

### *Complete Replacement*

11.9 The most obvious targets for Replacement are the established animal methods used to comply with testing regulations or standard operating procedures for the toxicity testing of chemicals and biological medicines. Considerable effort has been directed to replacing these tests, such as the Draize eye-irritancy test in rabbits (see Box 11.2). Complete Replacement of these procedures has not yet been achieved, although *in vitro* tests are being increasingly used to identify strongly irritant and corrosive chemicals, so that animal tests are not required to screen out these compounds.[6]

#### Box 11.2: The Draize test

Developed in 1944, the Draize test, along with the $LD_{50}$ (paragraph 9.14) is an animal test for toxicity. It involves placing the tested substance directly into the eye of a live, conscious animal and observing the results. The test is usually performed using albino rabbits. In 1999, 3500 Draize tests were undertaken. The test has been recently replaced by alternative approaches and in 2003 a total of 33 eye tests, including Draize and other tests, were undertaken.*

Many people are concerned that the Draize test causes suffering and it has received much attention from animal protection groups. Some scientists also claim that the test is invalid because of differences between the human and rabbit eye. Rabbits have a third eyelid, a thinner cornea, a more alkaline eye than the human eye, and produce less tear fluid to wash away irritants.† It is claimed that the Draize test overestimates how irritating a product is to the human because rabbits' eyes are more sensitive. The test is also thought by some to be imprecise because it is purely observational. The toxicity is evaluated by an investigator rather than quantitatively measured.‡

The Draize test is still widely used in the USA. In the UK it is no longer used for the testing of cosmetic products and ingredients, following the ending of animal testing for cosmetics. However, it is still used as a safety test for non-cosmetic products and chemicals, and is recommended for regulatory risk assessments of chemicals and a range of manufactured products that may be deliberately or accidentally brought into contact with the eyes.∫ The Home Office has published guidance for the test. These include the following stipulations: testing should only take place when *in vitro* screening tests have been used to identify, classify and eliminate materials with obvious irritant potential; it should not be carried out with strongly acidic or alkaline substances, nor with substances which are already known to produce severe adverse effects on the skin.** In response to a study which claimed that a variety of valid alternatives existed,†† the Home Office concluded in 2001 that the currently available alternatives to the Draize test had significant limitations and were not suited to replace live animal use.‡‡ Research aiming to develop alternatives to the Draize test continues. This includes, for example, the use of human eye tissue obtained from tissue and organ donors, and protein solutions that can be manufactured to be sensitive to potential irritants.∫∫

* Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (London: HMSO).

† Kaufman SR (1989) *Problems with the Draize Test. Perspectives On Animal Research,* Vol. 1, available at: http://www.curedisease.com/Perspectives/vol_1_1989/Problems%20with%20the%20Draize.html. Accessed on: 16 Jun 2004.

‡ The Group for the Education of Animal Related Issues

*Continued*

5 The pyrogen test is used to determine whether a substance is fever inducing. The test involves injecting a sample of the substance being tested, usually into rabbits. The rabbits must be individually held in a fixed position for a number of hours in a cage. Through temperature probes placed in the rectum of the animal, increased temperature is measured and, if recorded, gives an indication of pyrogen contamination. 3R Research Foundation Switzerland, 3R Training: *Rabbit in vivo pyrogen test*, available at: http://3r-training.tierversuch.ch/content.php?ctool_page_id=134&lang=en. Accessed on: 6 May 2005; Liebsch M (1995) History of the LAL-test: validation and regulatory acceptance *ALTEX* **12**: 76–80.

6 See OECD (2001) *Series On Testing And Assessment, Number 33: Harmonised Integrated Classification System For Human Health And Environmental Hazards Of Chemical Substances And Mixtures: ENV/JM/MONO(2001)6*; Chapters 2.2 (Skin Irritation/Corrosion) and 2.3 (Eye Irritation/Corrosion), available at: http://www.oecd.org/LongAbstract/0,2546,en_2649_34365_2671862_1_1_1_1,00.html. Accessed on: 6 May 2005.

(GEARI), available: http://www.geari.org/faqdraize.html. Accessed on: 16 Jun 2004.

∫ See European Commission *Directive on dangerous substances 67/548/EEC, Directive on plant protection products 91/414/EC and Directive on medicinal products for human use 2001/83/EC* and their UK counterparts.

** Statement by Secretary of State for the Home Department, House of Commons. Hansard Written Answers for 16 Jan 2001 (pt 21), available at: http://www.parliament.the-stationery-office.co.uk/pa/cm200001/cmhansrd/vo010116/text/10116w21.htm. Accessed on: 16 Jun 2004.

†† Wilhelmus KR (2001) The Draize eye test *Surv Ophthalmol* **45**:493-515.

‡‡ Statement by Secretary of State for the Home Department, House of Commons. House of Commons (2001) Hansard Written Answers for 16 Jan 2001 (pt 21), available at: http://www.publications.parliament.uk/pa/cm200001/cmhansrd/vo010116/text/10116w21.htm. Accessed on: 6 May 2005.

∫∫ For example, EpiOcular developed by the Mattek Corporation, available at: http://www.mattek.com/pages/products/epiocular Accessed on: 16 Jun 2004; the Irritection Assay system developed by Invitro International, available at: http://www.invitrointl.com/products/irritect.htm. Accessed on: 16 Jun 2004; the Agarose Diffusion method, Cottine M *et al.* (1993) Critical evaluation of an Agarose Diffusion method for the assessment of eye irritancy *ATLA* **21**: 427–40, available at: http://altweb.jhsph.edu/publications/journals/atla/atla21_4/atla21_4b.htm. Accessed on: 16 Jun 2004; see also Draize FAQ The Group for the Education of Animal Related Issues (GEARI), available at: http://www.geari.org/faqdraize.html. Accessed on: 16 Jun 2004.

11.10 A major success in the use of Replacements in toxicity testing was achieved in 2000, when, following a successful validation led by ECVAM (Box 2.5 and paragraph 11.32), an *in vitro* test for phototoxicity[7] was adopted as a standard test guideline by the EU, and two years later by the OECD.[8] In basic biomedical research there are also examples of where Replacement methods have successfully been applied to established methods or techniques in a particular research field. For example, monoclonal antibodies were usually produced in mice (by the ascites method (see paragraph 5.25) before *in vitro* methods were developed. Here, the deployment of a non-animal alternative method can be seen as complete Replacement.

### *Non-animal techniques as 'advanced' methods*

11.11 Animal experiments are often only one part of a scientific study or programme of research. For example, developing an effective vaccine against West Nile virus, a fatal infection of horses transmitted by mosquitoes, includes the following: molecular studies of the virus, studies of virus growth and development in insect and mammalian cell lines, epidemiological studies of vector populations and disease incidence in the field, mathematical modelling of the transmission and spread of disease, and clinical studies. This work usually involves very little experimental live animal use. Some laboratory infection of horses (or small-animal models) is undertaken to examine the progression of the disease in a controlled manner, to discover the exact means of insect transmission and to develop and test candidate vaccines. In this case, the molecular and epidemiological studies are not *Replacements* for the animal work; they are addressing *different scientific questions* within the research programme.

11.12 The terms 'advanced' or 'complementary' have been applied to many non-animal methods (for example, the molecular biology and mathematical modelling techniques mentioned above) to indicate that these methods have been developed to answer specific scientific questions that animal tests cannot address. They were not developed exclusively to replace animals for ethical reasons, and it is therefore unhelpful to refer to them in claims that all animal research could easily be replaced, if there was only a will to do so.

7 While a medicine by itself may have no toxic effects, this may change in combination with light. Phototoxicity studies test whether the toxic properties of a compound change when exposed to light. This is important if a compound is applied to a specific area of the body that may be exposed to light, in the form of a skin cream for example. A phototoxic compound may enhance the possibility of ultraviolet (UV) light inducing skin cancer. TNO Nutrition and Food Organisation *Phototoxicity: the combined effect of sunlight and pharmaceuticals on skin*, available at: http://www.voeding.tno.nl/ProductSheet.cfm?PNR=ZE_226A. Accessed on: 29 Apr 2005.

8 Animal tests for phototoxicity carried out before this date could in principle have been replaced by the alternative method. The new test did not in fact replace an existing EU or OECD test guideline for an animal test until 2000/2002.

### *Non-animal methods as adjuncts*

11.13 Non-animal methods may act as an adjunct to animal experiments rather than replace them, but in so doing, they may serve to reduce the total number of animals used in a programme of work. A classic example is the screening of anti-cancer drugs in nude[9] mice with human tumours. An initial screen using cell cultures can be used to demonstrate basic tumour cytotoxicity, and only the active toxins are tested *in vivo*. The same principle is used in high-throughput screening of potential medicines (see paragraph 8.6). This approach involves testing a large range of potentially useful candidate chemicals for a particular purpose in non-animal systems (especially computer prediction studies and *in vitro* tissue culture) using techniques that can be carried out very rapidly. Those chemicals with desirable biological activity (efficacy) and devoid of undesirable activity (toxicity) can then be selected for further study. In this way, it is possible to reduce the numbers of animal tests required to assess a given number of chemicals. The severity of animal tests can be minimised by screening out substances that are likely to be toxic at an early stage. In recent years, high-throughput screening has become widely adopted by the pharmaceutical industry (see paragraphs 8.4–8.6).

### *Alternative approaches*

11.14 Another equally important concept is the use of an *alternative approach* to an experimental goal enabling the *avoidance* of animal use. Even where there are no obvious alternatives, any proposed scientific study should consider at an early stage not only whether the animal experiment is the most appropriate and only method of addressing each research question, but also whether the question is worth asking, and whether it justifies causing pain and suffering to a sentient animal. In other words, the first alternative to consider is the option not to carry out the experiment at all. For example, within the REACH testing programme (see Box 9.2) the first consideration might be whether a particular test is actually necessary, regardless of whether there are, for example, adjunct Replacement methods that could be used in research.

## The potential for Replacement of animals in different areas of research

### *Toxicity testing required by regulation as a special case*

11.15 There is a tendency for discussion on the potential for replacing animals to focus solely on toxicity testing required by regulation and efficacy testing (which comprises around 16 percent of all animal use in science). Tests for regulatory purposes have received the most obvious and specific attention with respect to the development of Replacements.[10] Two factors have been influential in this respect: first, over the past 30 years public concern about the types of substances tested, such as cosmetics, household products and chemicals, and the type of tests carried out has increased (for example, the $LD_{50}$ and Draize tests; see paragraph 9.14 and Box

9 'Nude mice' are mice born without any T lymphocytes, which means that they effectively have no immune responses.

10 The British Toxicology Society (BTS) produced a report on the use of *in vitro* methods for toxicity testing in 1997, see Fielder R, Atterwill CK, Anderson D *et al*. (1997) British Toxicology Society (BTS) Working Party Report on *in vitro* toxicology *Hum Exp Toxicol* **16**: S1–40. The Third FRAME Toxicity Committee has also published a comprehensive discussion on the development of replacement methods for toxicity testing over the last decade, see Combes R, Schechtman L, Stokes WS and Blakey D (2002) The international symposium on regulatory testing and animal welfare: recommendations on best scientific practices for subchronic/chronic toxicity and carcinogenicity testing *ILAR J* **43**, Supplement: S112–17; see also Salem H and Katz SA (1999) *Toxicity Assessment Alternatives – Methods, issues, opportunities* (Totowa, NJ: Humana Press); Castell JV and Gómez-Lechón MJ (Editors) (1997) *In vitro Methods in Pharmaceutical Research* (London: Academic Press); Knight DJ and Breheny D (2002) Alternatives to animal testing in the safety evaluation of products *Alternat Lab Anim* **30**: 7–22; Combes RD (2002) The ECVAM workshops: a critical assessment of their impact on the development, validation and acceptance of alternative methods *ATLA* **30**, Supplement 2: 151–65.

11.2)[11]. Secondly, the nature of these tests suggests that it is easier to make progress in this field, as toxicity testing required by regulation asks defined questions and tends to involve a limited number of standardised tests, which are repeated (on different chemicals) many times. There is also an established institutional structure for the validation of alternatives (see paragraph 11.32).

11.16 Most toxicity testing required by regulation is carried out by industry which has devoted considerable resources and managed effort to the development and implementation of Replacements. These developments have occurred partly in response to activities by animal protection organisations, and partly because many alternative approaches are developed as 'advanced methods' to solve specific problems (paragraph 8.42). Added impetus has recently been given by the amendment of the EU Cosmetics Directive[12] to impose a marketing ban on cosmetics that have been tested or have had any of their ingredients newly tested on animals.

11.17 Standard test methods are also used in the safety and efficacy assessment of biologicals, including vaccines. The technical problems in replacing these tests are quite different from those encountered in the testing of chemicals. Further efforts are required to develop and validate methods that allow replacement of the use of animals, particularly in highly distressful challenge tests (see paragraph 8.24 and Box 8.5).[13]

## Biomedical research

11.18 In contrast to tests for safety and efficacy, the development of Replacements to current uses of animals in biomedical research is generally perceived as more difficult. The scientific questions that are addressed in biomedical research are more diverse and open-ended, with less-predictable outcomes. Moreover, the animal model itself is often the focus of the research (see Chapters 6 and 7). The objectives and designs of biomedical research projects are extremely diverse. It may sometimes be possible to identify certain basic, widely used techniques that would be amenable to replacement of animals. The replacement of the ascites method of production of monoclonal antibodies is one such example (see paragraph 5.26). In general, however, opportunities for replacement or avoidance of animal use in every project need to be explored on a case by case basis, with due regard to the specific objectives and the scientific barriers to the use of non-animal methods.

## Barriers to developing Replacements and how these could be overcome

11.19 There are some general principles regarding the constraints on the development of Replacements. These are well documented in the case of toxicity testing required by regulation[14] but many of the same principles apply to biomedical research. We now consider some general features of scientific and non-scientific barriers to developing Replacements. In Chapter 15 (paragraphs 15.61–15.67) we set out recommendations about how they might be overcome.

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11 See The Boyd Group (1998) *The use of animals for testing cosmetics: A discussion paper from the Boyd Group*, available at: http://www.boyd-group.demon.co.uk/cosmetics.htm. Accessed on: 29 Apr 2005; The Boyd Group (2002) The *use of animals in testing household products: A discussion paper and statement of principle*, available at http://www.boyd-group.demon.co.uk/householdproducts.pdf. Accessed on: 29 Apr 2005.

12 European Commission (2003) Directive 2003/15/EC of the European Parliament and the Council *Official Journal of the European Union* 11 March 2003.

13 See Hendriksen CFM, Spires J-M, Akkermans A *et al*. (1998) Validation of Alternative Methods for the Potency Testing of Vaccines: ECVAM Workshop Report 31, *ATLA* **26**: 747–61, and Weissler K and Hechler U (1997) *Animal Welfare Aspects in the Quality Control of Immunobiologicals: A critical evaluation of the animal tests in Pharmacopoeial Monographs* (London: FRAME).

14 European Commission (2004) *Opinion of the Scientific Committee on Toxicity, Ecotoxicity and the Environment on The BUAV-European Coalition to End Animal Experiments Report: The Way Forward – Action to End Animal Toxicity Testing*, available at: http://europa.eu.int/comm/health/ph_risk/committees/sct/documents/out217_en.pdf. Accessed: 26 Apr 2005.

***Scientific barriers***

11.20 There are scientific obstacles to developing relevant and reliable non-animal methods that can mimic the complex integrated physiological systems of humans and others animals. It is extremely difficult, using computational or *in vitro* systems, to take account of factors such as:

- The diversity of different tissues and cell types that make up a living organism; hundreds of different cell types at various stages of development may function and respond in different ways, or to different degrees.
- The ways in which cells and tissues interact, both locally and via the bloodstream and nervous system; immune reactions, germ cell development, metabolism and many other normal and disease-related processes involve extensive interaction between cells of different types and in various locations in the body.
- The influence of tissue organisation on the cellular environment; oxygen levels, rate of nutrient supply, intercellular communication and barrier formation all affect how cells behave and respond to external stimuli.

11.21 In research involving human volunteers, the scientific constraints are quite different, and usually secondary to ethical considerations. They include problems caused by variability (genetic and lifestyle) in the human population, the difficulty of controlling environmental variables such as diet and health over long periods, and the slow rate of human reproduction. Although human variability is an intrinsic facet of the very subject of medical research, there are occasions when it makes the design of conclusive scientific studies on humans impossible (see paragraph 10.33).

11.22 Scientific barriers to Replacement are likely to be more difficult to overcome in some areas of research than in others, and need to be considered on a case by case basis. To make further progress, there is an obvious need for scientific research to find ways of overcoming obstacles, and to develop non-animal techniques capable of addressing scientific questions about how biological systems work, how they are altered in disease, and how they are affected by chemicals and medicinal products.

***Non-scientific barriers***

11.23 Scientific obstacles are not the only limiting factors in replacing animal research. There are other possible constraints that may impede the implementation of Replacements. They include: regulatory inertia, insufficient funding, non-availability of human tissue, lack of incentives to explore the potential of Replacements, lack in the availability of information about suitable Replacements, insufficient integration of *in vitro* and *in vivo* research, and the possibility that tradition and conservatism may mean that researchers are reluctant to explore the potential of Replacements.

Regulatory inertia

11.24 Regulatory agencies have the crucial role of ensuring the safe use of products such as industrial chemicals, pharmaceuticals or vaccines. A very complex and intensely bureaucratic regulatory system has evolved to achieve adequate protection of humans, animals and the environment. The introduction of Replacements for established animal tests is therefore not straightforward. Regulatory authorities can be reluctant to depart from methods which they have traditionally relied upon for safety and liability requirements. The international regulatory authorities also need to be convinced that the alternative methods which are available and accepted in particular countries provide an adequate assessment of risk. Intensive efforts are needed to facilitate and accelerate the validation and regulatory acceptance of Replacements through bodies such as the OECD and ICH, as well as ECVAM

and the European Commission (see paragraphs 11.32 and 15.84–15.87).

### Funding

11.25 It is difficult to estimate accurately the amount of funding that is spent on research into Replacements. This is partly because funds are more commonly made available for all Three Rs rather than specifically for Replacement. Research is often directed towards developing specific techniques that, although they may have potential as Replacements, are envisaged as advanced methods rather than targeted specifically at replacing animals. There is a small number of charities such as FRAME, the Dr Hadwen Trust, the Lord Dowding Fund and the Humane Research Trust (see Boxes 2.3 and 2.4) that are dedicated to funding research on Replacements, but their budgets are limited.[15] More recently, major research funding bodies, such as the MRC, the Biotechnology and Biological Sciences Research Council (BBSRC), and the newly established NC3Rs, have offered limited funds for research specifically dedicated to the development of Replacements (see Box 11.3). The pharmaceutical and chemical industries have already invested comparatively large sums in research on Replacements, particularly in toxicology, and seem likely to increase that investment.[16] An initiative has also been established by the cosmetics and chemical industries, which seeks to fund development of Replacements in a limited number of specific regulatory tests.[17]

### Availability of human tissue

11.26 Controversy surrounding issues of informed consent have highlighted ethical constraints on obtaining human tissue for research. In the UK, concerns about the unauthorised retention of human tissue and organs at a number of hospitals led to the drafting on new legislation to regulate their use.[18] The draft provisions of the Human Tissue Bill were criticised by a range of stakeholders who feared that difficulties in both recruiting volunteers and gaining access to human tissue for use in non-animal research would be increased.[19] However, revisions made in light of the ensuing discussion appear to have met most of these.

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15 See *FRAME* website, available at: http://www.frame.org.uk. Accessed on 29 Apr 2005; *Dr Hadwen Trust* website, available at: http://www.crueltyfreeshop.com/drhadwen/about.htm. Accessed on 29 Apr 2005; *The Lord Dowding Fund for Humane Research* website, available at: http://www.navs.org.uk/research/about/ldf.htm. Accessed on 29 Apr 2005.

16 The ABPI estimates that the UK-based pharmaceutical industry spends in excess of £300 million annually on the development of non-animal methods, see Association of the British Pharmaceutical Industry (2003) *Alternatives to the use of animals in medicines research*, available at: http://www.abpi.org.uk/press/media_briefings_03/2003/Brief_%20Ani.pdf. Accessed on 29 Apr 2005.

17 Major companies of the chemical, pharmaceutical and cosmetic industry are in the process of establishing an International Partnership for Alternatives to Animal Testing (IPAAT). So far, there are three Working Groups focusing on developing Replacements for tests which are currently used in lung (inhalation) toxicity, repeat-dose toxicity/toxicokinetics and risk assessment strategies. The companies directly involved in these Working Groups are BASF, Cognis, DuPont, Henkel, L'Oreal, Novozymes, Pfizer, P&G, TNO and Unilever. In the field of respiratory (immuno)toxicity a first joint project is expected to commence in late 2005. Personal communication Dr Erwin Roggen (Novozymes AS), 27 April 2005.

18 NHS Retained Organs Commission (2002) Retention and use of human tissue and organs (London: DoH); see also Furness P and Sullivan R (2004)The Human Tissue Bill *BMJ* **328**:533-4

19 See also Home Office (2004) *Human Tissue Act 2004*, available at: http://www.legislation.hmso.gov.uk/acts/acts2004/20040030.htm. Accessed on: 29 Apr 2005; Nuffield Council on Bioethics (2004) *Human tissue: ethical and legal issues – Response from the Nuffield Council on Bioethics to the Human Tissue Bill*, available at: http://www.nuffieldbioethics.org/fileLibrary/pdf/ncob_response_-_ht_bill.pdf; European Commission (2004) *Directive 2004/23/EC of the European Parliament and of the Council on setting standards of quality and safety for the donation, procurement, testing, processing, preservation, storage and distribution of human tissues and cells*, available at: http://europa.eu.int/comm/health/ph_threats/human_substance/tissues_en.htm. Accessed on: 29 Apr 2005.

Incentives

11.27 Biomedical researchers are usually under pressure to achieve results and solve problems quickly. A number of factors are likely to influence this pressure: these include a genuine urgency to understand and alleviate human or animal suffering and a competitive environment that frequently makes research grants dependent on publication activity. In either case, researchers may be reluctant to spend time on developing non-animal alternative methods when it appears that an available animal method will give publishable results. In addition, the development of alternative methods may be perceived as having a lesser status than research. We consider ways of improving the recognition of the development of Replacements from within the academic research community in paragraph 15.61.

Availability of information

11.28 Fundamental to identifying alternative approaches is the availability of adequate information on past and current research in specific fields (see paragraph 11.34). Accessing information about suitable Replacements or alternative approaches to particular scientific questions can be difficult as such information is not always published. Even if it is published, the information is not usually indexed so as to highlight any of the Three Rs (see paragraph 15.58).

Integration of *in vitro* and *in vivo* research

11.29 *In vitro* toxicology, as distinct from *in vivo* toxicology, has become a science in its own right and there may be a risk that the primary goal of replacing animals can be overlooked. Some commentators are concerned that there is insufficient communication between scientists working *in vivo* and *in vitro*. They fear that *in vitro* toxicologists are becoming overly focused on methodological issues and the development and application of new techniques, gradually losing contact with the mainstream *in vivo* research in their original field. Such a shift could mean that valuable information on alternative techniques is not available to those who could apply them, because it is not published in journals relevant to their research interests or presented at the meetings that they attend. Others counter that it is problematic to make generalising statements in this area, asserting that, for example, in the pharmaceutical industry, there is a high degree of coordination and exchange of information.

Tradition and conservatism

11.30 Most scientists whose work involves animals are comfortable with the concept of Reduction and Refinement, although members of the Working Party also reported from personal experience that knowledge about the potential for Refinement varied. They had sometimes experienced hesitancy from other scientists in entering into serious discussion about the potential for replacing animals in their own field of research. If researchers have always used animals and are working in a field that has historically relied substantially on animal research, a change in methodology may not be straightforward, as it is common for scientists to frame research objectives in light of the means available. The creation of opportunities for appropriate lateral thinking is likely to require more than 'better training', and it may be useful to explore ways of achieving structural and institutional change which allow researchers to reconsider ways in which specific research questions can be answered by non-animal methods (see paragraph 15.60). This approach could be especially relevant to research fields such as experimental physiology and experimental biology, which have always depended very substantially on the use of whole, living animals and where the only alternative may be not to do the experiment. Questioning the justification for an entire research programme is, understandably, not something that comes

easily to most researchers. This is particularly so in a climate where technological advances such as biotelemetry are continually pushing the boundaries of what is possible in fundamental physiology, and scientists are under increasing pressure to fully exploit these techniques. Hence, the concept of Replacements might be regarded by some researchers as either completely irrelevant or as a direct attack on their life's work.

## Making progress – some national and international activities

11.31 Over the past decades, a number of organisations have been established which seek to coordinate efforts in relation to the promotion of Replacements. We briefly summarise them below.

### *Coordination of effort*

11.32 The ECVAM was established by the European Commission in 1993, for the express purpose of undertaking research into alternative methods and facilitating and organising their validation (see Box 2.4). ECVAM now works with its US counterpart, the Interagency Co-ordinating Committee on the Validation of Alternative Methods (ICCVAM). These organisations have been concerned primarily with validating Replacements in regulatory safety testing. In this regard, ECVAM has been working with the European Directorate for the Quality of Medicines[20] on the development of alternative methods for testing vaccines, and with the Test Guidelines Programme of the OECD for chemicals. The OECD has recently admitted observers from animal protection organisations to its meetings on test methods for chemicals testing via the International Council on Animal Protection in OECD Programmes (ICAPO).

11.33 A number of European countries have national organisations, or platforms, that are coordinated by ECOPA, the European Consensus Platform and which seek to promote the application of alternatives. Some of the member organisations, such as The Netherlands' Centre for Alternatives, are well-established institutions involving government, academia, industry and animal-welfare organisations in a variety of activities including commissioning research and providing information on alternative methods. In ECOPA, the UK is represented by the Boyd Group which, although it has members from the four main sectors mentioned above, is not primarily a centre for alternatives. The UK has recently established a centre dedicated specifically to the Three Rs (see Box 11.3).

### Box 11.3: UK National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs)

In July 2002 a House of Lords Select Committee published a Report on Animals in Scientific Procedures which recommended, among other things, the establishment of a national centre for the Three Rs. This was envisaged as a small, administrative hub to coordinate research units embedded in existing centres of scientific excellence. Several stakeholders commented on the recommendation, including the Dr Hadwen Trust and the Lord Dowding Fund, who published a joint proposal, suggesting that the national centre should focus on Replacements only.*

In April 2004, the UK Government announced the establishment of the *UK National Centre for the Replacement, Refinement and Reduction of Animals in Research* (NC3Rs).† The Centre aims to provide a focus for the promotion, development and implementation of the Three Rs in animal research. It replaces and builds upon the Medical Research Council's Centre for Best Practice for Animals in Research (CBPAR). The NC3Rs will fund Three R-related research, develop a range of information resources and guidelines, and organise workshops and symposia to disseminate and advance information about the Three Rs. The Centre's ultimate aim is the Replacement of animals in research, but it recognises that as long as animals continue to be used in research it is essential that every effort is made to reduce numbers of animals used, and to refine as far as possible the procedures in which they are involved.

* Dr Hadwen Trust and Lord Dowding Fund (2002) A national centre for the replacement of animals in experiments. A proposal by Lord Dowding Fund and Dr Hadwen Trust, see http://www.navs.org.uk/download_files/news/NationalCentreProposal.pdf.

† 10 Downing Street (2004) Welfare drive for animal experiments 21 May. Press release available at: http://www.number-10.gov.uk/output/Page5851.asp. Accessed on: 16 Jun 2004. See also: http://www.nc3rs.org.uk/. Accessed on 21 April 2005.

20 This organisation is part of the European Pharmacopoeia, operated by the Council of Europe.

***Information on Replacements, education and training***

11.34 Many organisations provide information on Replacement methods in research and education. For example, ECVAM provides an online database, the ECVAM Scientific Information System (SIS), which provides details of methods currently undergoing validation[21] and, in Germany, the German Institute of Medical Documentation and Information (DIMDI) Center for Documentation and Evaluation of Alternative Methods to Animal Experiments (ZEBET) gives access to a database called Animalt-Zebet, which has extensive information on Replacements.[22] A bibliographic database (Altbib) is maintained by the US National Library of Medicine.[23]

11.35 The provision of information in tertiary and postgraduate education has long been promoted by the RSPCA and is now being pursued in conjunction with the Boyd Group. Interniche has produced a comprehensive guidebook to educational alternatives[24] and there are web-based information services, such as the European Union Resource Centre for Alternatives in Higher Education (EURCA)[25] and the Norwegian Reference Centre for Laboratory Animal Science and Alternatives (NORINA).[26]

## Summary

11.36 In this chapter we have explored the concept of the Replacement approach, and its current and future applications. We differentiated between *complete* Replacement, which relates to alternative methods that do not involve any use of animals, or animal tissue or organs, and *incomplete* Replacement, where either early developmental stages of animals or animal tissue, for example of humanely killed animals, is used. We argued that the concept of Replacement is best understood in a broad sense. We also discussed several different ways in which non-animal methods can be used: on the one hand, they can *replace* existing tests; on the other they may *displace* or *avoid* animal experiments altogether. Non-animal methods may also function as advanced methods, or as adjuncts to animal experiments.

11.37 The public debate about the potential for replacing animals usually focuses on what is or is not possible with animal experiments in general. This is not particularly helpful or constructive. We observed that the potential for achieving Replacement of animals depends on the nature of the specific scientific question being addressed and therefore has to be evaluated on a case by case basis rather than in general terms. Similarly, claims about whether or not Replacements are more economic, faster or produce more reliable scientific data need to be assessed in the same way. Accordingly, we considered a range of approaches where Replacements are currently being used, including computer studies, *in vitro* methods and human studies.

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21 ECVAM *Scientific Information Service*, available at: http://ecvam-sis.jrc.it/. Accessed on: 6 May 2005.

22 German Institute of Medical Documentation and Information (DIMDI) Center for Documentation and Evaluation of Alternative Methods to Animal Experiments (ZEBET) *Animalt-Zebet*, available at: http://www.dimdi.de/static/en/db/dbinfo/dbmemo/zt00eng.html. Accessed on: 6 May 2005.

23 National Library of Medicine *ALTBIB: Bibliography on Alternatives to the Use of Live Vertebrates in Biomedical Research and Testing*, available at: http://toxnet.nlm.nih.gov/altbib.html. Accessed on: 6 May 2005.

24 Jukes N and Chiuia M (2003) *From Guinea Pig to Computer Mouse*, 2nd Edition (Leicester: International Network for Humane Education).

25 European Resource Centre for Alternatives in Higher Education (EURCA) website, available at: http://www.eurca.org. Accessed on: 6 May 2005.

26 Norwegian Reference Centre for Laboratory Animal Science & Alternatives (NORINA) website, available at: http://oslovet.veths.no. Accessed on: 6 May 2005.

11.38 There is a tendency for discussion on the potential for replacing animals to focus solely on toxicity testing required by regulation, and it appears that most progress has been made in this area. In order to explore the potential for replacing animals elsewhere, scientific and non-scientific barriers that can influence the implementation of Replacements need to be considered. These include the high degree of complexity of human biological processes, which is relevant where animals are used for the study of human disease; possible reluctance by regulators to accept new alternative methods; access to human tissue; and the scientific standing of research that aims to develop Replacements. We return to ways of overcoming these obstacles in paragraphs 15.57–15.62 and now turn to the current state and future potential of Refinement and Reduction.

# Chapter 12

## Reduction and Refinement

# Reduction and Refinement

## Introduction

12.1 In the previous chapter we discussed the opportunities and current limitations of the first of Russell and Burch's Three Rs, the Replacement approach. We now turn to the remaining two concepts Refinement and Reduction, which need to be considered whenever the use of animals to achieve a scientific objective is deemed unavoidable. As we have said, the Three Rs are closely interrelated.[1] The relationship between Reduction and Refinement is particularly evident when these principles are applied at the early stage of research projects to improve research strategy as a whole. We first give brief consideration to this relationship and then examine Reduction and Refinement more closely as individual concepts. The role of harmonising international test guidelines for the purpose of reducing animal research is then explored before we focus on the potential of Refinements. We give examples of how to implement Refinements in specific areas of research and also consider possible barriers.

## Applying Reduction and Refinement to research strategies

12.2 Animals will suffer needlessly if they are used in research where scientific methodology is poor. In such cases, research does not achieve its scientific objectives, and fails to generate significant knowledge. It is for this reason that the application of the Three Rs should begin with a careful assessment of the initial experimental design and be continued throughout the duration of each and every research project. This process requires a number of basic questions to be addressed at a very early stage. For example, is the chosen animal model sufficiently relevant to the scientific question being asked or health problem under study? Is there a genuine scientific basis for using a particular animal model? Could the scientific question itself be refined? Could the scientific objective of the work be modified to avoid the use of an animal model? The following three general approaches are relevant to the successful implementation of Reduction and Refinement at this stage of research.

- **Background research**: it is essential that a thorough search of the published literature is undertaken to ensure that the proposed experiments have not already been undertaken and the objectives of the research have not already been met by previous well-conducted experiments. Part of this survey of the literature should be an assessment of the validity of the conclusions of previous studies. New experiments should not be based on unsound conclusions drawn from poorly designed experiments.
- **A staged approach**: before embarking on large or complex experiments the project should be broken down into a series of pilot experiments, with defined decision points that inform the transition from one stage to another. A small pilot experiment on animals or *in vitro* research can be very useful in guiding the design of subsequent, larger experiments. For example, an initial pilot study might help define experimental parameters early on, so that fewer animals could be used later. It might also be possible to refine experiments so that suffering and the number of animals used is reduced by carrying out pilot experiments on anaesthetised animals that are not allowed to recover.
- **Teamwork and resources**: the successful completion of an experiment depends on many factors, including the skills and performance of the staff involved, and the availability of suitable equipment and facilities. Optimal experimental design and successful application of the Three Rs requires a multidisciplinary approach with contributions from biomedical

[1] Russell and Burch themselves acknowledged that there was overlap between the Three Rs; see Russell WMS and Burch RL (1959) *The Principles of Humane Experimental Technique* (London: Methuen).

scientists and animal care staff, statisticians, information scientists and other specialists such as biochemists, geneticists and clinicians. Lack of adequate staff training and expertise and the use of unreliable equipment can lead to failed projects and the fruitless use of animals.

12.3 These are just some of the crucial factors that need to be taken into account when considering whether the use of animals can be justified. The goal should be to design each experiment or overall project plan in such a way that it causes the least amount of suffering to the minimum number of animals, at the lowest level of neurological development. As we have said, this goal is an integral part of UK legislation (see paragraph 3.59). We have also emphasised that it is not sufficient to simply follow rules; researchers must strive actively for best practice (paragraph 3.69). The continued application of Refinement and Reduction before, and throughout the duration of a research project is especially relevant in this context. We note that doubt has been expressed in a recent Report by the House of Lords Select Committee about the effort that is put into these approaches.

> 'We are not, however, persuaded that enough effort is always made to avoid the use of animals. We are similarly not persuaded that where this is possible, sufficient effort is always made to minimise the number of animals used, and to minimise the pain and suffering inflicted on each animal.'[2]

We consider next ways in which the application of Refinement and Reduction can be improved.

## Reduction

### *Definition and scope*

12.4 Russell and Burch initially defined Reduction as 'reduction in the numbers of animals used to obtain information of a given amount and precision'. More recently, this definition has been developed to state: 'the use of fewer animals in each experiment without compromising scientific output and the quality of biomedical research and testing, and without compromising animal welfare'.[3] The proviso that Reduction should not compromise animal welfare is necessary because reduction in the number of animals used can sometimes be achieved by performing more procedures on each animal. This could cause an undesirable increase in the suffering of individual animals. In addition to improved research strategy, as outlined above, Russell and Burch suggested two additional ways in which animal use could be reduced: better control of variation and better statistical analysis.

- Reducing variation: choice of appropriate animal species and strains

  Many factors need to be considered in choosing the most appropriate animal model for a particular experiment. Thus, for example, the species, strain, sex and age of the animals are all important criteria. The outcome of a project may depend critically on the strain(s) used. A wide range of inbred strains, mutants, outbred stocks and transgenic strains of mice and rats are available. The use of genetically more uniform or inbred stocks, if appropriate to the particular experiment, may reduce variation and therefore allow the use of fewer animals.

- Statistics and experimental design

  A lack of understanding of the basic principles of statistical methods can lead to

2 House of Lords Select Committee (2002) *Animals in Scientific Procedures* (Norwich: TSO).

3 Festing MF (1994) Reduction of animal use: experimental design and quality of experiments *Lab Anim* **28**:212-21; Festing MFW, Baumans V, Combes RD, *et al*. (1998.) Reducing the use of laboratory animals in biomedical research: Problems and possible solutions *ATLA* **26**:283-301.

inappropriate analysis of experimental results and to the conduct of experiments which yield results that are not even amenable to proper statistical analysis. A survey of 78 experiments, described in papers published in two leading toxicology journals between 1989 and 1990, showed that over 60 percent had obvious statistical errors. About one third of the experiments involved far more animals than necessary to achieve the stated aims of the research.[4] Where statistical analysis is crucial to the outcome of a research project, it is vital that careful consideration is given to the design of experiments to take account of the degree of variation to be expected, the required statistical power, and the method of statistical analysis to be used. Ways of improving experimental design by controlling variability and allowing the use of more-sophisticated statistical methods have been suggested.[5] One way of using these methods in practice would be to improve training of scientists; a more practical and reliable option may be to ensure that scientists have the opportunity to consult at an early stage with a statistical expert.

12.5 The two approaches above are of special relevance for ensuring that numbers of animals intended to be used in a specific research project are reduced as far as possible. But Reduction also has another dimension in the sense that it is desirable to reduce the total number of experiments which are undertaken. In this context, data sharing is an important means of avoiding duplication of testing in toxicology as well as pharmaceutical and academic research. In the case of toxicology testing and pharmaceutical research the results of tests are often commercial property, and the need for confidentiality may sometimes lead to duplication of testing. In basic research, duplication[6] may occur when researchers are unaware that a particular experiment or test has already been carried out by other researchers. There have been claims and counter-claims about the extent to which studies are duplicated.[7] Nevertheless, ensuring that results from research are shared as much as possible is a useful way of reducing the total number of animals involved in research. The principal way in which data are currently shared is by publication of research in peer-reviewed journals. However, not all research actually undertaken is published. Some therefore argue that it would be desirable to ensure greater availability of reports of 'negative', or unsuccessful, research results.[8] But there are problems in publishing research findings that are not peer reviewed. The peer-review process helps to ensure that only findings from properly conducted research are published, and publication of poorly conducted research may lead to confusion.

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4 See also Festing MFW (1996). Are animal experiments in toxicological research the "right" size? in *Statistics in Toxicology* Morgan BJT (Editor) (Oxford: Clarendon Press), pp3-11; Festing MFW and Lovell DP (1996) Reducing the use of laboratory animals in toxicological research and testing by better experimental design *J R Stat Soc* **58**: 127-140; see also: Editorial: Statistically significant (2005) *Nat Med* **11**: 1.

5 See Festing MF (1990) Use of genetically heterogeneous rats and mice in toxicological research: a personal perspective *Toxicol Appl Pharmacol* **102**:197-204; Festing MF (2001) Guidelines for the design and statistical analysis of experiments in papers submitted to ATLA *Altern Lab Anim* **29**:427-46; Festing MF (2002) The design and statistical analysis of animal experiments *ILAR J* **43**: 191-3; Festing MF and Altman DG (2002) Guidelines for the design and statistical analysis of experiments using laboratory animals *ILAR J* **43** 244-58; Shaw R, Festing MF, Peers I and Furlong L (2002) The design and statistical analysis of animal experiments *ILAR J* **43**:191-3; Howard BR (2002) Control of variability *ILAR J* **43**: 194-201.

6 It is important to distinguish between *duplication* and *replication* of experiments, see paragraph 15.16.

7 See, for example BUAV (2001) BUAV *Submission to the House of Lords Select Committee on Animals in Scientific Procedures*, available at: http://www.buav.org/pdf/BUAV_HOL_Evidence.pdf. Accessed on: 9 May 2005; see also Home Office (2005) *Report by the Animal Procedures Committee (APC) Review of the cost benefit assessment in the use of animals in research: Government Response by Caroline Flint MP, Parliamentary Under-Secretary of State for the Home Department*, available at: http://www.homeoffice.gov.uk/docs4/jw280305flint_banner_report_by_the_animal_procedures_committee.pdf. Accessed on: 9 May 2005.

8 See paragraphs 35-37 of Animal Procedures Committee (2001) *Report on openness*, available at: http://www.apc.gov.uk/reference/openness.pdf. Accessed on: 9 May 2005.

12.6 In the UK, in 2002 the inter-Departmental Group on the 3Rs[9] was formed, as a successor to the Inter-Departmental Data Sharing Group, which produced and published in 2000 the inter-Departmental Data Sharing Condordat. The Concordat is a voluntary scheme which seeks to 'promote opportunities for encouraging agencies, industry and other stakeholders to endorse the principle of data sharing and to extend its scope by looking to overcome the practical, legal, commercial and cultural barriers to its effective implementation.'[10] Among other things, the Concordat encourages minimisation of data requirements for tests as far as possible, and the reviewing of procedural and legal barriers to data sharing. Under the Concordat, 'UK regulatory authorities, as lead agencies, [will] press for agreement on behalf of the UK Government for fullest provisions and procedures which enable data sharing when negotiating, updating and transposing relevant European Directives and when taking part in other international harmonisation processes.' We return to issues raised by the possible duplication of research in different areas in Chapter 15, where we reconsider the national and international context of research (paragraphs 15.68–15.70 and 15.83). We also explore ways in which the avoidance of duplication can be ensured especially in relation to research involving GM animals (paragraphs 15.71-15.75).

***Harmonisation of international test guidelines***

12.7 We have noted that many tests involving animals are conducted to provide safety or efficacy data for regulatory authorities, in compliance with national or international legislation (see paragraphs 9.4 and 13.48). If different authorities require testing to be carried out using their own specific study designs, a single chemical that is marketed in a number of countries might need to be tested several times for toxic effects. Harmonisation of test guidelines, so that a single study design is acceptable to regulatory authorities in many countries, is a very valuable means of reducing the number of animals used in safety and efficacy testing worldwide. Harmonisation has many advantages: it can reduce the need for repeat testing; eliminate the requirement for redundancy in testing (where more than one test provides the same information); minimise group sizes (e.g. by agreement to use a single sex) and lead to the adoption of shortened protocols, reduced animal numbers and less-severe treatments and procedures.

12.8 A relatively high level of harmonisation of test methods for chemicals has been achieved by the Test Guidelines Programme of the OECD. Similarly, in the area of pharmaceuticals, the ICH has achieved a substantial decrease in the numbers of animals used globally in the pre-clinical safety assessment of new pharmaceuticals (about a 50 percent reduction overall for a typical package of tests).[11] Examples of reduction in regulatory testing include:

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9 The Group is led by Home Office officials and has members from the Department of Health, the Department for the Environment, Food and Rural Affairs, the Department of Trade and Industry, the Office of Science and Technology, the Food Standards Agency, the Health and Safety Executive, the Medicines and Healthcare Products Regulatory Agency and other agencies. Its terms of reference are 'to improve the application of the 3Rs and promote research into alternatives, reducing the need for toxicity testing through better sharing of data, and encouraging the validation and acceptance of alternatives.' See http://www.homeoffice.gov.uk/docs2/interdept3rs.html. Accessed on: 3 May 2005.

10 Home Office (2002) *The Inter-Departmental concordat on data sharing*, available at: http://www.homeoffice.gov.uk/docs/dataconcordat.html. Accessed on: 3 May 2005; see also Animal Procedures Committee (2003) *Review of the cost-benefit assessment in the use of animals in research* (London: HO), p52-6.

11 The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions to discuss scientific and technical aspects of product registration. The purpose is to make recommendations on ways to achieve greater harmonisation in the interpretation and application of technical guidelines and requirements for product registration, in order to reduce the need to duplicate the testing carried out during the research and development of new medicines; Lumley CE and van Cauteren H (1997) Harmonisation of international toxicity testing guidelines for pharmaceuticals: contribution to refinement and reduction in animal use *EBRA Bulletin* November: 4–9.

- As discussed in Chapter 9, the 'classical' $LD_{50}$ test was used for many years to estimate the oral toxicity of a single dose of a chemical (paragraph 9.14). Although a few $LD_{50}$ tests are still used in some circumstances, widespread and enduring opposition to this test on animal-welfare grounds led to the development of several alternative methods in which fewer animals were dosed, in a stepwise manner.[12]
- Tiered testing strategies have been employed to reduce the use of animals in several areas of toxicity testing. For example, the irritancy of chemicals for the skin and eye was previously assessed by using rabbits, without any prior testing. The currently recommended procedure involves assessing the chemical properties of the test materials and the use of *in vitro* methods as a first stage. Assessment of skin irritancy is undertaken before the eye test. Only if none of the previous assessments indicate irritancy is the eye test performed on live rabbits.[13]
- Vaccines that are produced from living organisms (e.g. viruses and bacterial toxoids) are tested for safety and/or efficacy at a number of points during manufacture, and batches are usually tested more than once to ascertain their efficacy (Box 8.5). These tests involve the use of large numbers of animals, and often involve infecting both vaccinated and unvaccinated animals with the relevant pathogen, leading to severe suffering in some unprotected animals.[14] Some of these 'challenge tests' for vaccine potency can be replaced with serological methods in which the presence of specific antibodies in the blood of immunised animals is used to demonstrate protection against challenge by the pathogen. A major success of this approach has been the development and validation of serological methods for the potency testing of tetanus vaccines, which have reduced the number of animals required.
- Prompt deletion of obsolete or redundant tests from testing requirements is a high priority for avoiding unnecessary use of animals. For example, tests for abnormal toxicity, which were general tests for adverse effects of vaccines, have been deleted from most monographs of the European Pharmacopoeia. Also, two types of animal test that were previously required for toxicity testing of diphtheria and tetanus vaccines have been eliminated. Substantial reductions in the number of animals used per batch have been achieved by modifications to five other tests on diphtheria, tetanus and pertussis vaccines.[15]

## Refinement

### *Definition and scope*

12.9 The original definition of Refinement by Russell and Burch was 'any decrease in the incidence or severity of inhumane procedures applied to those animals which still have to be used [in experiments]'. This definition[16] has been modified to encompass the positive

12 The Fixed Dose Procedure (FDP) uses approximately one quarter of the animals required by the $LD_{50}$ test. FDP avoids the death of the animals as an endpoint, recording signs of "evident toxicity" instead. The Up-and-Down Procedure (UDP) is a stepwise approach where one animal receives the dose thought to be the best estimate of the $LD_{50}$ dose. Depending on the outcome (death/life), the dose for the next animal is adjusted. After reaching the reversal of the initial outcome (i.e. the point where an increasing or decreasing dose pattern is reversed by giving a smaller or higher dose) four additional animals receive the dose, to replicate the finding. UDP requires more time than the previous methods and is more expensive, but uses fewer animals; See *Test Guideline No 420: Fixed Dose Method and Test Guideline No 425: Up-and-Down Procedure* in OECD (2001) *Guidelines for Testing of Chemicals* (Paris: OECD).

13 Guideline 405 Acute eye irritation/corrosion in OECD (2001) *Guidelines for Testing of Chemicals* (Paris: OECD).

14 Associate Parliamentary Group for Animal Welfare (2005) *The use of animals in vaccine testing for humans*, available at: http://www.apgaw.org/userimages/Vaccinetesting.pdf. Accessed on: 9 May 2005.

15 Associate Parliamentary Group for Animal Welfare (2005) *The use of animals in vaccine testing for humans*, available at: http://www.apgaw.org/userimages/Vaccinetesting.pdf. Accessed on: 9 May 2005.

16 Refinement is sometimes referred to incorrectly as 'the refinement of experiments to get more data'. This is clearly an important goal, but it is not an interpretation of Refinement as originally defined in the Three Rs.

concept of improving welfare as well as of reducing suffering, and to encompass husbandry and care as well as procedures. Reducing suffering and improving animal welfare are important for the following four reasons:

- First, as discussed in Chapters 3 and 4, it is clear that animals can suffer and that their suffering needs to be taken seriously.
- Secondly, societal concerns about the use of animals, and acceptance of different uses, appears to depend to a considerable degree on the amount of suffering experienced by animals.
- Thirdly, both the physical and psychological welfare of laboratory animals has a significant effect on the experimental results. For example, sympathetic nervous system (SNS) activity is significantly increased in mice housed in stressful conditions such as social deprivation. The SNS controls many different body systems including the immune and gastrointestinal systems. Any change in SNS function will therefore have widespread effects on the animals and on their physiological responses that will effect experimental data.[17]
- Fourthly, the law controlling experiments on animals requires animal suffering to be minimised.

Thus, aside from the moral and legal requirement to reduce and prevent suffering, good animal welfare is consistent with good science and also ensures the effective use of resources, and animals.

***Potential for Refinement***

12.10 Of all the Three Rs, Refinement to reduce suffering and improve welfare is probably the easiest to achieve in the short term for all types of animal use, as highlighted in the following response to the Consultation:

> 'It is attractive, and undoubtedly important, to focus a great deal of effort on the development of Replacement methods. However, it is important that expectations about the scope for replacement with non-animal methods should not be unrealistic and that focus on Replacement should not be at the expense of efforts for Refinement. The potential for improvements through Refinement – making animals' lives better through better husbandry, better research techniques, and better veterinary methods to alleviate discomfort and stress – should not be underestimated.'
> *UFAW*

12.11 However, in order to achieve maximum effect, it is essential to be aware of the kind of Refinements available and how best to implement them. Since Refinement concerns the reduction of suffering, a crucial prerequisite is to be able to recognise what causes, or is likely to cause, animals to suffer (see Chapter 4). As we have noted, there are many sources of potential suffering throughout the lifetime of each animal which may need to be considered in addition to those resulting from scientific procedures and their effects (paragraphs 4.49–4.59).

***Some specific examples of Refinement***

12.12 Further to the discussion in Chapter 4, we now consider examples of four especially important areas in which Refinement can be implemented: housing, husbandry and care, experimental procedures, pain management and humane endpoints.

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17 Gentle MJ (2001) Attentional shifts alter pain perception in the chicken *Anim Welfare* **10**: S187–94.

## Refining housing, husbandry and care

12.13 Laboratory animals spend most of their time in cages or pens, so their immediate environment, and the care they receive, has a major impact on their well-being. Standards for laboratory housing are defined in the Home Office Codes of Practice for the husbandry and care of animals[18] and corresponding European guidelines.[19] These represent minimum standards only and are mainly concerned with satisfying the physiological rather than the behavioural needs of the animals. For example, rats are social animals that, in the wild, have large home ranges, eat a varied diet and exhibit a range of complex behaviours.[20] Yet according to current guidelines for laboratory animals, two adult rats can be kept for the whole of their life in a cage with a floor area of 700 $cm^2$ (the size of a large shoe box) containing a few millimetres of sawdust and perhaps a tube to hide in (see also Box 12.1). Unmodified, this is a very confined and barren environment.

12.14 Refinement of laboratory animal husbandry requires the provision of an 'enriched' environment that satisfies not only the physiological, but also the behavioural needs of the animals and these have to be identified for each species and strain. One way of doing this is to use the results of behavioural studies, which measure an animal's preference for, or motivation to obtain, a particular resource, such as a nest box for chickens, access to social companions in rats, and rooting materials for pigs (see Box 4.2).

12.15 It is easier to identify the needs of some species than others. In the case of rats and mice there is a significant scientific literature on their behavioural needs. Similarly, nesting material, facilities for animals to hide, and material for gnawing are fundamental requirements for both rats and mice.[21] It is therefore relatively straightforward to ascertain from the scientific literature what the laboratory environment must provide in order to try and satisfy the basic needs of rats and mice.[22] Important aspects of Refinement for rodent husbandry are listed in Box 12.1.

### Box 12.1: Husbandry – needs of mice and rats

A good-quality environment providing for a range of activities would include:

- housing in stable, compatible groups;
- enough space for exercise and to perform normal social behaviour;
- a solid floor with a wood-shaving substrate;
- height to accommodate rearing (up to 30 cm in an adult rat);
- nesting material;
- material to gnaw; and
- refuges.

18 Home Office (1989) *Code of Practice for the Housing and Care of Animals Used in Scientific Procedures* (London: HMSO). See also the supplementary codes which concern a range of more specific research contexts, available at: http://www.homeoffice.gov.uk/comrace/animals/legislation.html#codes. Accessed on: 9 May 2005.

19 European Community (1986) *Council Directive 86/609 on the Approximation of Laws, Regulations, and Administrative Provisions of the Member States Regarding the Protection of Animals Used for Experimental and Other Scientific Purposes*, OJ L.358. (Luxembourg: EC).

20 See Berdoy M (2003) *The Laboratory Rat: A Natural History*, available at http://www.ratlife.org. Accessed on: 3 May 2005.

21 See Fillman-Holliday D and Landi MS (2002) Animal Care Best Practices for Regulatory Testing *ILAR J* V43 Supplement; Sherwin CM (2002) Comfortable quarters for mice in research institutions, available at: http://www.awionline.org/pubs/cq02/Cq-mice.html. Accessed on: 9 May 2005; Lawlor MM (2002) Comfortable quarters for rats in research institutions, available at: http://www.awionline.org/pubs/cq02/Cq-rats.html. Accessed on: 9 May 2005.

22 Chmiel DJ and Noonan M (1996) Preference of laboratory rats for potentially enriching stimulus objects *Lab Anim* **30**: 97–101; Manser CE, Elliott HE, Morris TH and Broom DM (1996) The use of a novel operant test to determine the strength of preference for flooring in laboratory rats *Lab Anim* **30**: 1–6; Townsend P (1997) Use of in-cage shelters by laboratory rats *Anim Welfare* **6**: 95–103; Patterson-Kane EG, Hunt M and Harper DN (1999) Behavioural indexes of poor welfare in laboratory rats *J Appl Anim Welfare Sci* **2**: 97–110.

12.16 Once species-specific needs have been identified, ways of satisfying the animals' needs in a laboratory setting may be developed. Further to improving the welfare of animals and the quality of scientific results, implementations of Refinements have the benefit that animals housed with a good quality and quantity of space are frequently easier to handle and work with. Research shows that rats group-housed in enriched environments are quicker to learn new tasks, less stressed, more confident, less aggressive and in better general condition than singly housed animals. Such benefits can improve staff morale and encourage further exploration of opportunities to implement all Three Rs.

Refining experimental procedures

12.17 As we have illustrated in Chapters 5-9, a very wide variety of experimental procedures is applied to laboratory animals, from those that are relatively minor, such as blood sampling, through to major surgery. The procedures themselves may cause adverse effects (paragraph 9.28) and there may also be adverse effects as a result of a procedure (paragraph 4.54). For this reason it is crucial to consider what opportunities there are to refine every aspect of each procedure from start to finish. One particular category of procedures where there is great potential for Refinement is the administration of substances to animals.[23] Such procedures are required for many experiments, for example to create a disease in order to study it, to test the effectiveness of a new medicine, or to assess the toxicity of a chemical. There is a variety of techniques employed for such purposes, and in each case it is important to think about Refinement with respect to the animal's immediate experience of the administration method and all that it entails. This assessment should include any distress from necessary handling and restraint (see paragraphs 4.44–4.47), as well as from the administration method itself. The substance administered can also have a profound effect on the animal in the short and long term. For example, it may irritate the animal's nose or stomach, or cause nausea or seizures.

12.18 The potential for Refinement may be understood better in considering a specific example, such as the injection of a substance into an animal's joint to study arthritis (see paragraph 6.7) or to ascertain the efficacy of medicines to treat the disease. This procedure can be very painful and has the potential to cause swelling, inflammation and infection of the joint, and consequent lameness. Refinement of the technique encompasses several elements. The needles used for injection must be the smallest size possible and the volume of the substance given and frequency of dosing should also be kept to a minimum so as not to distend the joint. The animal needs to be kept calm and held very still and the operator has to have a good knowledge of the anatomy of the joint. The procedure should only be done once and to one joint only. If all these Refinement aspects are fully implemented, the animals will suffer far less pain. The guiding principle in this, and in any other aspect of Refinement, is never to assume that current practice is best practice, and to review all the techniques and protocols that are used at regular intervals. One helpful approach in devising possible improvements can be to think about a technique from the animal's point of view and to ask how a specific procedure would feel if it were applied to oneself. While this suggestion is not intended to encourage uncritical anthropomorphism (see paragraph 4.3) it can be a helpful tool in reviewing current practice in view of species-specific needs.

Refining the management of pain

12.19 Reducing any pain associated with experiments is another important aspect of Refinement. Success depends critically on the ability of those dealing with the animals to recognise and

23 Morton DB, Jennings M, Buckwell A *et al.* (2001) Refining procedures for the administration of substances *Lab Anim* **35**: 1–42.

assess pain and suffering (paragraphs 4.18–4.30). Most people involved with animal use are confident of their ability to detect the relevant signs, but some staff are insufficiently trained and lack the relevant expertise.[24] Special training is required because many laboratory animals are adapted to conceal signs of pain or distress (see paragraph 4.12). Most people can recognise and respond to overt clinical signs of moderate to severe pain in laboratory animals, but it can be more difficult to recognise indicators of mild to moderate discomfort, pain or distress, which can be very subtle and hard to detect. For example, audible vocalisation is still often cited as a sign that rats are in pain, yet it is now widely known that rats usually vocalise ultrasonically. For truly effective Refinement, these subtle signs of suffering also need to be identified so that staff can become familiar with them. For example, in the case of rats undergoing abdominal surgery, recent research has shown that behaviours such as flank twitching can be used to identify whether rats require more pain relief.[25] Until this research was carried out, few if any guidelines on pain assessment for rats mentioned this behaviour, yet it occurs regularly and is highly diagnostic. This approach requires rigorous evaluation of animal behaviour and an open mind.

12.20 It is important to appreciate that Refinement is a continuous process and not a static formula that is only applied at one stage. Ideally, research establishments should have a framework in place for regularly reviewing the way in which experiments are conducted, and comparing current practice with new evidence emerging from research on animal behaviour. This can allow for the development of improved methods of managing pain. A proactive establishment would provide any or all of the following measures as appropriate in its pain management programme:

- pre-emptive pain relief as well as post-operative pain relief;
- multi-modal pain therapy using different pain relieving medicines, which work in different ways and therefore achieve improved control of pain;[26]
- husbandry and care in the spirit of critical anthropomorphism, which addresses species-specific needs (paragraph 4.30);
- staffing (of appropriate expertise) at such levels as will enable the need for intervention (whether treatment or euthanasia) to be anticipated.

Refining endpoints

12.21 The vast majority of animals are killed at the end of the experiment, either because their tissues are required as part of the experiment, or because the scientific objectives have been achieved and the animal can no longer be used. However, under UK law there is provision for limited and tightly controlled re-use, or release of animals to the wild, or a home, where this is appropriate for the individual animal.[27] If the experiment leads to an increasing amount of suffering during its course then it is best for the animals to be killed as early as possible. This approach is described as operating 'humane endpoints' and requires indicators of likely suffering to be detected at an early stage. For example, if it is known that particular clinical signs such as decreased body temperature lead to a specific outcome such as death, then animals can be killed as soon as these signs appear. Other markers that can

24 See, for example, Flecknell P and Karas A (2004) Assessing and Managing Pain and Distress for Ethics Committees *ATLA* **32** Supplement 1: 265–6.

25 Roughan JV and Flecknell PA (2001) Behavioural effects of laparotomy and analgesic effects of ketoprofen and carprofen in rats *Pain* **90**: 65–74.

26 Multimodal pain therapy is the combined administration of opioid and non-opioid pain relief.

27 See A(SP)A Schedule 14 and 15, the options of release of animals to the wild, an abattoir or a home are chosen very rarely.

be used to define humane endpoints include flank twitching (paragraph 12.19) and chemical and haematological changes in the blood.[28]

12.22 But in some cases the only way to determine the clinical signs indicating that animals should be euthanised may be to allow some animals to suffer considerably or even die, carefully recording the clinical signs throughout their lives so that a retrospective analysis can be undertaken. This approach has been used successfully to refine some of the protocols required for toxicity testing of vaccines.[29] Humane endpoints should generally be easier to define within safety-assessment programmes because routine procedures are used and the only variable is, for example, the batch of vaccine.[30]

***Barriers to implementing Refinement***

12.23 We have observed above that implementation of Refinements is usually more straightforward than Reduction and Replacement and that many Refinements have been developed by scientists during the normal course of their work. There should in fact be fewer scientific barriers to Refinement. Where they do occur, it can be difficult to determine whether they are real or perceived and exactly what the nature of the barrier is. One common concern is that the provision of Refinement in the form of environmental enrichment may add unwanted variables that may reduce the validity of experimental data. For example, in toxicology it might be argued that giving wooden chews to animals affects their metabolism and interfers with the results. This may mean that more animals have to be used to generate statistically significant results. However, there are usually ways around such problems, for example, by using commercially available enrichments that have been fully characterised and standardised.

12.24 Other, non-scientific, barriers to the application of Refinement can result from:

- limited understanding of the concept of Refinement, why it is important and when and how to apply it;
- limited understanding of the species-specific needs of animals, causes of suffering and the impact of laboratory research and housing on the full lifetime experience of an animal;
- lack of specific information and guidance on practical Refinements, relating to what to do and how to do it;
- lack of resources, including time and funds; and
- lack of motivation and training.

12.25 All of these factors can significantly limit the implementation of Refinement, which, in view of its relative ease of application and its great potential for reducing suffering, is regrettable. Nevertheless, many establishments in the UK are very proactive with regard to Refinement and, taking animal husbandry as an example, have good, innovative environmental enrichment programmes. But there is also anecdotal evidence that some researchers argue that animals 'do not do anything', and therefore do not need anything

28 See Hendriksen CFM and Morton DB (Editors) (1999) *Humane Endpoints in Animal Experiments for Biomedical Research*. Proceedings of the Int Conference, 22–5 Nov 1998, Zeist, The Netherlands. (London: Royal Society of Medicine).

29 Johannes S, Rosskopf-Streicher U, Hausleithner D *et al*. (1999) Use of clinical signs in efficacy testing of erysipelas vaccines, in *Humane Endpoints in Animal Experiments for Biomedical Research*. Proceedings of the Int Conference, 22–5 Nov 1998, Zeist, The Netherlands, Hendriksen CFM and Morton DB (Editors) (London: Royal Society of Medicine), pp102-105; Krug M and Cussler K (1999) Endotoxin in porcine vaccines: clinical signs and safety aspects, in *Humane Endpoints in Animal Experiments for Biomedical Research* Proceedings of the Int Conference, 22–5 Nov 1998, Zeist, The Netherlands, Hendriksen CFM and Morton DB (Editors) (London: Royal Society of Medicine), pp114–17.

30 See also: Hendriksen CFM and Morton DB (Editors) (1999) *Humane Endpoints in Animal Experiments for Biomedical Research*. Proceedings of the Int Conference, 22–5 Nov 1998, Zeist, The Netherlands. (London: Royal Society of Medicine).

to do. Such judgements point to limited knowledge of animal behaviour because the converse is often true. Animals that have nothing to do tend not to do anything.

12.26 Some problems in promoting Refinements arise from the fact that species-specific needs are not well characterised. Even when they are, as in our earlier example of rats, available knowledge is not always applied. For example, grid floors instead of solid floors may be used in some establishments without specific scientific justification and important resources such as substrate and nesting material are not universally provided. In a survey published in 2001, up to 25 percent of rats received no nesting material, up to 35 percent were not given anything to gnaw and over 50 percent were not provided with refuges, all of which play a significant role in relation to promoting the well-being of rodents.[31] The effectiveness with which pain is managed is also inconsistent as practice with regard to recognising and alleviating animal pain varies across different establishments and abilities of different people.[32]

12.27 Another significant barrier to the implementation of Refinement is the relative dearth of detailed and accessible information on, and practical examples of, Refinement. Relevant information tends to be found in journals on research techniques and animal welfare which are rarely consulted by researchers whose primary interest is in their own specialised research field. Useful information is provided by the reports of the Joint Working Group on Refinement (JWGR),[33] which provide practical advice on Refinement in husbandry of rabbits,[34] mice,[35] birds[36] and dogs;[37] and procedures including blood sampling,[38] administration of substances,[39] telemetry[40] and the generation and care of GM mice.[41] Lack of time and resources can also have implications for the implementation of enrichments and other Refinements, since such improvements require significant expenditure on staff and materials.

### *Overcoming constraints*

12.28 Thus, overcoming the constraints and improving the implementation of Refinement requires significant commitment to:

- an open-minded, innovative and proactive approach to developing new Refinements;
- seeking out available information on good practice and implementing it;

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31 Mortell N (2001) Practical environmental enrichment for rats and mice (the results of a survey) *Anim Technol* **52**: 1–19.

32 Richardson CA, Flecknell PA (2005) Anaesthesia and post-operative Analgesia Following Experimental Surgery in Laboratory Rodents: Are we making Progress? *ATLA* **33**: 119–127.

33 This group was set up by the BVA Animal Welfare Foundation (BVA/AWF), FRAME, the RSPCA and UFAW.

34 Morton DB, Abbot D, Barclay R *et al*. (1993) Removal of blood from laboratory mammals and birds *Lab Anim* **27**: 1–22; Morton DB, Jennings M, Batchelor GR *et al*. (1993) Refinements in rabbit husbandry *Lab Anim* **27**: 301–29

35 Jennings M, Batchelor GR, Brain PF *et al*. (1998) Refinements in mouse husbandry *Lab Anim* **32**: 233–59.

36 Hawkins P, Morton DB, Cameron D *et al*. (2001) Refinements in husbandry and procedures for laboratory birds *Lab Anim* **35**, Supplement 1: 1–163.

37 Prescott MJ, Morton DB, Anderson D *et al*. (2004) Refining dog husbandry and care: Eighth report of the BVAAWF/FRAME/RSPCA/UFAW Joint working Group on Refinement. *Lab Anim* **38** Suppl 1:1–94

38 Morton DB, Abbot D, Barclay R *et al*. (1993) Removal of blood from laboratory mammals and birds *Lab Anim* **27**: 1–22; Morton DB, Jennings M, Batchelor GR *et al*. (1993) Refinements in rabbit husbandry *Lab Anim* **27**: 301–29.

39 Morton DB, Jennings M, Buckwell A *et al*. (2001) Refining procedures for the administration of substances *Lab Anim* **35**: 1–42.

40 Hawkins P, Morton DB, Bevan R *et al*. (2004) Husbandry refinements for rats, mice, dogs and non-human primates used in telemetry procedures *Lab Anim* **38**: 1–10; Morton DB, Hawkins P, Bevan R *et al*. (2003) Refinements in telemetry procedures *Lab Anim* **37**: 261–99.

41 Robinson V and Jennings M (2004) Refinement and reduction in the production of genetically modified mice: Sixth report of the BVAAWF/FRAME/RSPCA/UFAW Joint Working Group on Refinement *ATLA* **32** Supplement 1: 373–5.

- knowing the animals' physiological and behavioural needs and being aware of current evidence on how to address these in the laboratory environment;
- anticipating expected *and* unintended adverse effects of all experimental work;
- being familiar with subtle signs of distress or discomfort in the species, strain, phenotype and individual animal, and knowing how to alleviate the cause;
- disseminating specific information on Refinement in an accessible way;
- publishing details of Refinement as an integral part of scientific papers in the mainstream literature; and
- most importantly, not assuming that *existing* practice is necessarily *best* practice.

## Summary

12.29 Effective implementation of Refinement and Reduction requires both concepts to be considered at an early stage to improve the general research strategy of a project. A staged approach before embarking on large or complex experiments is useful, starting with thorough background research of the published literature and considering the possibility of conducting a small pilot study. Effective teamwork also plays a significant role, involving staff with a wide range of relevant expertise, in for example *in vitro* technology, experimental design, statistics, and animal care.

12.30 We observed that the concept of *Reduction* is best understood as requiring 'the use of fewer animals in each experiment without compromising scientific output and the quality of biomedical research and testing, and without compromising animal welfare'. To improve its application, the importance of appropriate research strategies, better control of variation among animals, better statistical analysis and the avoidance of duplication need to be recognised. We considered successful examples of Reduction in regulatory testing and noted that harmonisation of international test guidelines can contribute significantly to further reduction.

12.31 *Refinement* is probably the most effective of the Three Rs in achieving immediate reduction of pain and suffering, and improvement of welfare of animals involved in research. The approach is of great relevance since reducing pain, suffering and distress is a crucial aspect of the moral debate about animal research, and a legal requirement. It is also important scientifically since the physical and psychological welfare of laboratory animals can have a significant effect on the scientific validity of experimental results.

12.32 Possibilities for implementing Refinement were considered in four areas: housing, husbandry and care, experimental procedures, pain management and humane endpoints. Refinement of housing conditions is particularly important since the quality of animals' cage or pen environments can have a major impact on their lives. While standards for laboratory housing are defined in the Home Office Codes of Practice for the husbandry and care of animals and relevant European guidelines, the requirements represent minimum standards. There should be relatively few scientific barriers to Refinement, and these should be considered on a case by case basis. A fundamental principle is never to assume that current practice is best practice. All the techniques and protocols that are used at regular intervals should be reviewed and critically assessed throughout the duration of any research programme. We present our conclusions and recommendations about the implementation of the Three Rs in Chapter 15 (paragraphs 15.57–15.62) and now turn to the regulation of animal research.

# Section 4

## Legal, ethical and policy related issues

# Chapter 13

## Legislation, regulation and policy relating to scientific procedures on animals

# Legislation, regulation and policy relating to scientific procedures on animals

## Introduction

13.1 In this chapter we consider the regulatory framework for research involving animals in the UK. We describe the historical background to the Animal (Scientific Procedures) Act 1986 (A(SP)A), its principal provisions and the three types of licence that it sets forth as requirements (personal licences, project licences and the certificate of designation for the establishment). We explain why the A(SP)A regulates 'procedures', rather than experiments, and how the severity of procedures is classified in regulatory terms. Having set out these general features, we describe how the Act is operated in practice. We consider the role of the Home Office Inspectorate, the Animal Procedures Committee (APC) and the institutional local Ethical Review Process (ERP). The way in which the cost-benefit assessment is undertaken and statistical data about the use of animals are presented are also reviewed. We go on to consider developments in regulation at the international level. Finally, UK and international regulation that either explicitly demands the use of animals for specific purposes, or sets out testing guidelines that are usually interpreted as requiring the use of animals are summarised (see paragraphs 8.22 and 9.4).

## Historical background to the A(SP)A

13.2 During the 19th century, legislation relating to animal treatment began to be enacted in the UK. The legal offence of animal cruelty was first introduced in An Act to Prevent the Cruel and Improper Treatment of Cattle ('Martin's Act'), passed in 1822. It stated that 'if any person or persons having the charge, care or custody of any horse, cow, ox, heifer, steer, sheep or other cattle, the property of any other person or persons, shall wantonly beat, abuse or ill-treat any such animal, such individuals shall be brought before a Justice of the Peace or other magistrate'. These provisions were extended in 1835 and 1849, before being consolidated in 1911 in the Protection of Animals Act, which forbade the causing of unnecessary suffering, making it a legal offence to 'cruelly beat, kick, ill-treat, over-drive, over-ride, overload, torture, infuriate or terrify any animal'.[1] By the First World War, domestic and captive mammals, birds, reptiles and fish were all generally protected from cruelty by law.

13.3 In addition, legislation was established to regulate the way in which animals were treated in specific circumstances. This included the Cruelty to Animals Act 1876, which related specifically to scientific experiments. It introduced the requirement of personal licences for those undertaking research and a system of inspection. From the 1960s onwards there was increasing criticism of the 1876 Act, and a series of official and semi-official committees made recommendations for changes to the law.[2] In addition, the European Directive EEC 86/609 required Member States to adopt national legislation, or similar legal instruments to implement its provisions. In the 1980s, the UK Government produced new draft legislation and eventually the 1876 Act was repealed by the A(SP)A.[3]

1 Radford M (2001) *Animal Welfare Law in Britain: Regulation and responsibility* (Oxford: Oxford University Press), Chapter 3.

2 Published reports include that of the Littlewood Committee in 1965, the House of Lords Select Committee on the Laboratory Animals Protection Bill (1980) and the Report of the Secretary of State's Advisory Committee on Animal Experiments (1981).

## The A(SP)A: general operational aspects

13.4 The A(SP)A[4] regulates the use of all vertebrate animals[5] (mammals, reptiles, amphibians, birds and fish) and, by a subsequent order in Parliament, the common octopus in 'any experimental or other scientific procedure...which may have the effect of causing that animal pain, suffering, distress or lasting harm'. These purposes are called 'regulated procedures' (see Box 13.1), and may only be undertaken if the Secretary of State has granted the necessary licences (see paragraphs 13.5–13.6).

### Box 13.1: Why does the A(SP)A use the term 'procedure' instead of 'experiment'?

The welfare of animals may not only be affected by the consequences of a particular scientific experiment but also by a range of other aspects of their lives. Since the A(SP)A seeks to regulate any activity that involves a protected animal and may cause pain, suffering, distress or lasting harm, the term 'procedure' was introduced to refer to the broad range of events that may affect animals. Thus, under the A(SP)A all aspects of the scientific experiment itself, as well as relatively minor interventions, such as the taking of a blood sample, are all termed regulated procedures and any research study will usually involve a number of these. Similarly, other scientific uses of animals, for example the testing of vaccines, or the use of animals for the production of biological products such as antibodies, are categorised as procedures, as well as the breeding of harmful mutants and GM animals (see paragraphs 13.14 and 13.25).

13.5 The regulatory scheme imposed by the A(SP)A is complex. There are absolute rules that, if broken, will lead to criminal liability. For example, it is a criminal offence to carry out what would qualify as a regulated procedure without the required licences. Such breaches are potentially punishable with an unlimited fine and imprisonment for a maximum of two years.[6] The Act also empowers the Secretary of State to make regulations (secondary legislation) to implement the principles embodied in the statute such as extending the categories of protected animals. Most crucially, the Act grants the Secretary of State extensive discretionary powers in relation to licensing research. This means that the Home Office necessarily develops, within limits, internal guidance and policy with regard to whether and on what terms requests for licences may be granted. The Act sets out the parameters within which discretion is exercised; and in practice they are applied on a case by case basis. So, for example, Section 5 (6) of the Act directs that 'The Secretary of State shall *not* grant a project licence authorising the use of cats, dogs, primates and equidæ[7] unless he is satisfied that animals of no other species are suitable for the purposes of the programme to be specified in the licence or that it is not practicable to obtain animals of any other species that are suitable for those purposes'. In more general terms, Section 5 (5) states that 'The Secretary of State shall not grant a project licence unless he is satisfied (a) that the purpose of the programme to be specified in the licence cannot be achieved satisfactorily by any other reasonably practicable method not entailing the use of protected animals'.

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3 In 1983, the Government produced a White Paper entitled *Scientific Procedures on Living Animals*. This Paper led to extensive consultation, and was followed by a supplementary White Paper with the same name, which appeared in 1985. The Bill that became the A(SP)A was based on the two White Papers. It was introduced in the House of Lords, where it was debated extensively and amended. The amended Bill then passed through the Commons with relatively little discussion.

4 Animal (Scientific Procedures) Act 1986 (A(SP)A), available at: http://www.archive.official-documents.co.uk/document/hoc/321/321-xa.htm. Accessed on: 4 May 2005.

5 Animals at early stages of development are excluded from the Act, see A(SP)A Section 1 (2) which states that: 'Any such vertebrate in its foetal, larval or embryonic form is a protected animal only from the stage of its development when (a) in the case of a mammal, bird or reptile, half the gestation or incubation period for the relevant species has elapsed; and (b) in any other case, it becomes capable of independent feeding.'

6 See A(SP)A Schedule 3 and 22. To inflict pain or suffering on an animal in the course of an unlicensed experiment could also involve criminal liability under the general law against cruelty to animals, contained in the Protection of Animals Act 1911, the Wild Mammals (Protection) Act 1996 and the Protection of Animals (Scotland) Act 1912, although the maximum penalties are lower.

7 The term 'equidæ' refers to the family that includes horses.

13.6 Subject to the general directions set out in the A(SP)A, the Secretary of State enjoys considerable discretion in the exercise of the statutory powers, including the development of both policy and administrative procedures.[8] For example, following an announcement by the Secretary of State before Parliament, the Home Office adopted a policy whereby licences for scientific procedures using animals to test cosmetics, or procedures that involve the great apes would not be issued.[9] The Secretary of State has thereby used the administrative powers to effect a *de facto* ban. Similarly, by attaching a standard condition to all certificates of designation that every establishment shall have a local ERP, this provision has become a mandatory requirement (paragraph 13.21).

13.7 Sections 19 and 20 of the A(SP)A established the APC, which was first appointed in 1987. The APC provides independent advice to the Secretary of State on any matters related to the A(SP)A as it sees fit or as may be referred to it by the Secretary of State (see Box 13.2 and paragraph 13.16).

### Box 13.2: The Animal Procedures Committee

The APC is composed of scientists, lawyers, veterinary surgeons, doctors, animal welfarists and philosophers. The Committee was established by the A(SP)A, which specifies that the Committee should comprise a chairman and at least 12 other members. At least two thirds of the members should have qualifications or experience in a relevant biological subject or have full registration as a medical practitioner or veterinary surgeon and at least one member should be a barrister, solicitor or advocate. The Act also states that the Secretary of State, responsible for appointments to the committee, should take into account the desirability of ensuring that the interests of animal welfare are represented. Usually one member of the Committee is an academic philosopher.

The A(SP)A specifies that the APC should have regard to both the requirements of science and industry and the protection of animals against avoidable suffering and unnecessary use. The Committee has the dual function of advising on certain licence applications when asked and independently advising on policy and practice. Most licence applications are assessed by the Home Office Animals (Scientific Procedures) Inspectorate (see paragraph 13.20). However, there are certain categories of project applications that the APC also considers, including those that involve the use of wild-caught primates and primates in procedures of substantial severity. The APC advises the Home Secretary on these applications, but does not itself decide on the outcome.

## The A(SP)A in practice

13.8 The A(SP)A requires that three separate licences, which are described in more detail below, must be obtained before any animal is used in a regulated procedure.

i) A personal licence authorises an individual to conduct specified regulated procedures on specified animal species, at a specified place or places. A personal licence by itself does not authorise a person to carry out any procedures. Rather, the authorisation may only be used in conjunction with two further licences (paragraphs 13.12–13.13).

ii) A project licence forms the centrepiece of the licensing process. This licence authorises individuals who hold a personal licence to conduct a particular programme of work, for specific purposes, at one or more specified designated establishments. It also describes the types of animals involved, the estimated numbers of animals that are intended to be used, the prospective severity banding of the project and individual severity limits for the protocols contained in it (paragraphs 13.14–13.18 and Box 13.3).

iii) A certificate of designation is issued to a person authorising a specified facility (called a 'designated establishment') to conduct animal procedures and/or breed or supply animals for use in regulated procedures (paragraph 13.19).

8 Such power may be exercised by the Secretary of State or by members of the Inspectorate acting on his or her behalf.

9 The use of great apes and the testing of cosmetics are not prohibited formally by law, but as a matter of policy. In principle, the policy could therefore be revoked at any time.

13.9 The Secretary of State may add conditions to any licences or certificates as considered reasonable and appropriate. A series of standard conditions are routinely added to every licence and certificate.[10] The Home Office employs Inspectors who assess all applications for licences and certificates and visit designated establishments to verify that procedures are conducted in accordance with the licences (see paragraph 13.20).

13.10 The Home Office also issues a *Code of practice on housing and care of animals used in scientific procedures* (published in 1989). It is widely agreed that the code does not identify best practice. Rather, it sets out the minimum standards expected of designated establishments, including minimum cage sizes, environmental conditions, animal health and welfare, and special considerations for individual species. Compliance with the code of practice is required by making it a condition of granting the certificate of designation. There are separate codes and guidelines for housing and breeding, as well as for animal euthanasia and a number of specific procedures.[11] As in the case of the *Code of practice on housing and care of animals used in scientific procedures*, these documents set out minimum standards.

13.11 The penalties for contravening the provisions of the A(SP)A, licences or certificates include formal admonitions, requirements for retraining, the placing of restrictions on licences, revocation of licences, fines and imprisonment.[12] Normally, the most effective deterrent is the Home Office's authority to revoke certificates or licences, which could have serious consequences for universities or pharmaceutical companies (in cases where certificates of designation are revoked), or individual scientists (where a project or personal licence is revoked, see Box 2.5).

***Personal licences***

13.12 Before a scientist or animal technician can be granted a personal licence, they must successfully complete a training course covering the legislation, ethical aspects of animal use, animal biology, husbandry, care and welfare and, where appropriate, surgery and anaesthesia. The licence is specific for the designated establishment(s) where research is to be conducted, and applicants must specify the animals for which they are seeking authority to use. The licence also lists the range of techniques to be used, such as giving injections, or carrying out specific types of surgery. The use of any other combination of species, technique or research location not specified in the licence is a legal offence. Personal

10 For example, since 1999, certificates have not been granted unless there is an ERP in place (see House of Commons (2002) *Guidance on the Operation of the A(SP)A 1986* (Norwich: Stationary Office)). Other standard conditions include the requirement that the establishment should be appropriately staffed at all times to ensure well-being of the animals (see *Guidance on the Operation of the A(SP)A 1986*).

11 See *Code of practice for the housing of animals in designated breeding and supplying establishments* (1995), *Humane killing of animals under Schedule 1 to the A(SP)A 1986* (1997) and *Housing and care of pigs intended for use as xenotransplant source animals* (draft). See Home Office website *UK and European legislation and guidance*, available at: http://www.homeoffice.gov.uk/comrace/animals/legislation.html. Accessed on: 1 Apr 2005.

12 The Home Office reports summary details of infringements to the APC, and information with respect to the cases reported are set out in the APC's Annual Reports. For example, in its Annual Report for 2002, the APC reported that the Home Office had revealed that there had been 20 'Class Three' (the most serious) infringements during the period November 2000–December 2001. The same report also specifically referred to research that had gone beyond licensed procedures and recorded: 'One such serious infringement [that impacted negatively on animal welfare] was reported to the Committee… This involved [loud] music being played to over 200 mice dosed with methamphetamine. Some of the mice were said to have suffered 'seizures' and at least 19 of them died as a result of the procedures. The study arose from a larger programme of work conducted as part of a licensed project concerning Huntington's disease, but it went beyond the procedures covered by the licence authorities. The infringement had come to light through the publication of a scientific paper on the work. …the project licensee had been admonished [by the Home Office] and required to undergo training; a personal licence holder had been admonished; and the certificate holder was asked to remedy defects in the record keeping systems in the department concerned.' No prosecution was brought and the APC noted that it was 'particularly concerned about this case'. In 2003, sanctions used by the Home Office were admonishment, ordering retraining and requiring reviews of operational procedures. Revocation of licences was recommended in two cases; both a licence and a certificate were voluntarily returned to the Home Office in advance of any formal action. Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (London: HMSO).

licences are not time-limited but are required to be reviewed at no more than five year intervals. Species or techniques may be added or removed in the course of the review.

13.13 The personal licence holders are obliged to ensure that any pain, suffering or distress to the animals is minimised and they bear primary responsibility for the welfare of the animals they use. Proper records must be kept for each project showing the number of animals used and the procedures that have been carried out, and giving information about the supervision of animals.

***Project licences and the cost-benefit assessment***

13.14 Project licences can only be granted for the following permitted purposes:

- 'the prevention (whether by the testing of any product or otherwise) or the diagnosis or treatment of disease, ill-health or abnormality, or their effects, in man, animals or plants;
- the assessment, detection, regulation or modification of physiological conditions in man, animals or plants;
- the protection of the natural environment in the interests of the health or welfare of man or animals;
- the advancement of knowledge in biological or behavioural sciences;
- education or training otherwise than that in primary or secondary schools;
- forensic enquiries;
- the breeding of animals for experimental or other scientific use'.[13]

13.15 The project licence has a number of functions, including:

- defining the objectives of the project;
- outlining the likely benefits of the project;
- describing the work to be conducted to achieve the objectives;
- listing the specific procedures to be used;
- identifying the likely adverse effects that may be experienced by the animals and how these will be avoided, recognised and alleviated; and
- placing an upper limit on the severity of the adverse effects to the animals (see Box 13.3 for how the severity of procedures is considered in the licensing process).[14]

### Box 13.3: How is the severity of procedures considered by the Home Office?

Severity to the animals involved is assessed prospectively, before a licence is granted. There are two main types of assessment, supplied by the licence applicant and evaluated by the Home Office, as follows.*

i) The *overall severity band of a research project* is intended to reflect the number of animals used on each protocol and the suffering likely to be caused as a result. It is based on the overall level of cumulative suffering expected to be experienced by each animal, rather than the single worst possible case. It takes into account the proportion of animals expected to reach the severity limit of the protocol and the duration of the exposure to that severity limit, the nature and intensity of the adverse effects, and the actions to be taken to relieve the suffering. It is therefore a qualitative and quantitative assessment of the anticipated *average suffering experienced by all the animals* used (see paragraph 15.27). In 2003, 39 percent of project licences were assigned

*Continued*

13 A(SP)A, Section 5 (3).

14 *Guidance on the Operation of the A(SP)A 1986*, Chapter 5, available at: http://www.archive.official-documents.co.uk/document/hoc/321/321.htm. Accessed on: 4 May 2005.

the mild category, 56 percent to the moderate category, three percent to the substantial category and two percent were unclassified (see below).

ii) The *severity limit* of individual *protocols* is determined by the maximum level of the expected adverse effects that may be experienced by an individual animal, taking into account the measures specified in the licence for avoiding and controlling adverse effects. It represents the worst possible outcome for any animal subjected to the protocol, even if it may only be experienced by a small proportion of the animals to be used.

A protocol is a procedure or a series of procedures carried out on an individual animal or group of animals for a single specific purpose within the context of the project. For most purposes, the protocol defines the individual steps or components of a regulated procedure,† usually in chronological order.

One of four levels of severity is assigned based on protocols that are:

**Mild**: includes procedures that give rise to slight or transitory minor adverse effects, including taking infrequent blood or tissue samples from an animal, and conducting skin irritation tests with substances that are expected to be non-irritant or mildly irritant.

**Moderate**: includes procedures such as injecting substances to produce antibodies, toxicity tests that do not involve lethal endpoints and many surgical procedures, provided that suffering is controlled and minimised by effective post-operative pain relief and care.

**Substantial**: includes procedures such as major surgery, toxicity testing leading to significant morbidity or death, and the use of some animals as disease models.

**Unclassified**: includes protocols in which animals are anaesthetised before a procedure starts and are killed at the end of the procedure without recovering consciousness.

The *Guidance on the Operation of the A(SP)A 1986* advises that the assessments of severity should be reviewed and revised as necessary during the lifetime of a project.

* *See: Guidance on the Operation of the A(SP)A 1986*, Chapter 5; Home Office (2005) *A(SP)A 1986 Application for a Project Licence*.

† See Box 13.1.

13.16 Section 5 (4) of the A(SP)A requires the Secretary of State to weigh the likely benefits from a project against the likely adverse effects on the animals.[15] In practice, this process is carried out by Home Office Inspectors who advise officials who in turn make the decision on behalf of the Secretary of State. This provision is frequently referred to as the 'cost-benefit assessment' (although the term is not itself used in the A(SP)A) and is widely regarded as the cornerstone of the way animal research is regulated in the UK (see paragraphs 3.58–3.61). While the ultimate decision on whether or not to grant a licence is made by the Secretary of State and his advisors, various other people and processes contribute to the cost-benefit assessment. A recent report by the APC, which examined in great detail the ways in which the cost-benefit assessment is, and should be, carried out, emphasised that *primary* responsibility for carrying out the assessment was held by the project licence holders.[16] The roles of other parties involved, such as the Home Office, the ERP and, where relevant, the APC, were described as 'to evaluate, advise, and in some cases adjudicate the researchers' own cost-benefit assessments' (see Figure 13.1).[17]

15 'In determining whether and on what terms to grant a project licence the Secretary of State shall weigh the likely adverse effects on the animals concerned against the benefit likely to accrue as a result of the programme to be specified in the licence.' See also *Guidance on the Operation of the A(SP)A 1986*, Appendix I, available at: http://www.archive.official-documents.co.uk/document/hoc/321/321-xi.htm. Accessed on: 6 May 2005.

16 See also *Guidance on the Operation of the A(SP)A 1986*, Appendix I, available at: http://www.archive.official-documents.co.uk/document/hoc/321/321-xi.htm. Accessed on: 6 May 2005.

17 Animal Procedures Committee (2003) *Review of the cost-benefit assessment in the use of animals in research* (London: Home Office), p77.

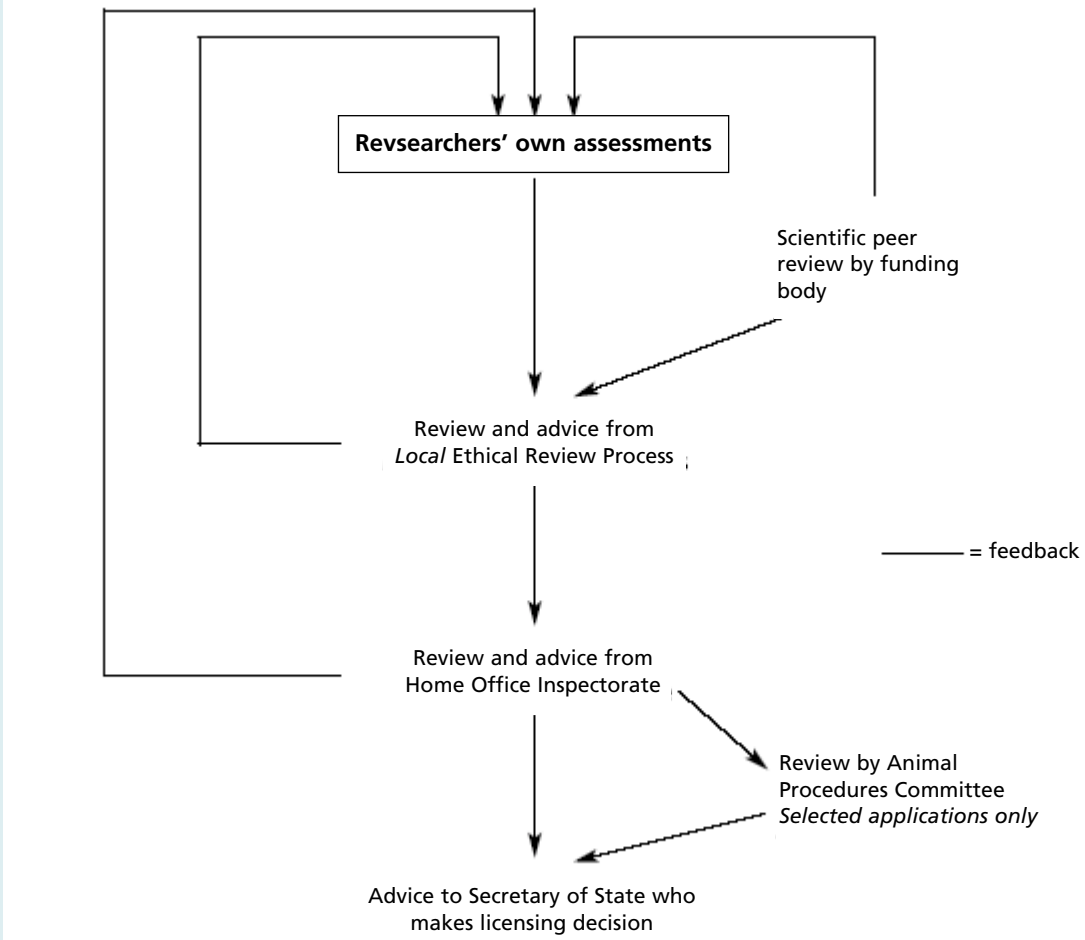


**Figure 13.1: Relationship between the different people and processes involved in cost-benefit assessment of applications for project licences***

* Animal Procedures Committee (2003) *Review of the cost-benefit assessment in the use of animals in research* (London: Home Office), p71.

13.17 A project licence is not granted unless the Secretary of State (as advised) is satisfied that:

- the purpose cannot be achieved by any other reasonable and practicable method which does not use regulated procedures on protected animals;
- the minimum number of animals will be used, with the lowest degree of neurophysiological sensitivity;
- the procedures to be used are those that will cause the minimum distress or suffering to the animals;
- procedures are conducted under anaesthetic wherever this can be used to reduce suffering, unless it would interfere with the objective of the experiment.[18]

Animals are not permitted to be used in more than one protocol except in those circumstances where it would result in less animal distress or suffering overall than starting a new protocol with a new animal, or when animals need to be used for a series of procedures for a particular purpose. Any reuse is subject to approval by the Secretary of

18 See A(SP)A, Section 5 (5); *Guidance on the Operation of the A(SP)A 1986*, Chapter 5, available at: http://www.archive.official-documents.co.uk/document/hoc/321/321.htm. Accessed on: 4 May 2005.

State (as advised). Section 14 of the A(SP)A provides that no animal that has been involved in protocols that caused severe pain or distress may be reused. Similarly, animals that have undergone procedures under general anaesthesia cannot be reused unless the Secretary of State has given permission and certain specified conditions are met.

13.18 Project licences last for a maximum of five years. The holder of a licence is personally responsible for all procedures conducted on animals under that licence. Project licences only give authority to perform those procedures stated in the licence. Contract research organisations are granted somewhat broader licences for toxicity testing. These might permit the testing of defined classes of, for example, pharmaceuticals or other chemicals to assess their effects on specific organs of specified animals, or they may be licensed to undertake particular types of research, for example on embryo or fetal development. In quantitative terms, licences may permit the conduct of many individual techniques, ranging from a few to several hundred. To conduct any procedures that vary from the specifications of the licence constitutes a breach of the law or the terms and conditions of the licence, and renders the licence holder liable to disciplinary action (see Box 2.5 and paragraph 13.11).[19]

***Certificates of designation***

13.19 The holder of the certificate of designation is normally expected to be a senior manager or official in the establishment. This individual is personally responsible for ensuring that the establishment complies with the conditions of the certificate. The certificate holder is also required to nominate at least one person who has day-to-day responsibility for the health and welfare of all the animals in their charge, called the named animal care and welfare officer (NACWO). A named veterinary surgeon (NVS) to advise the certificate holder, licence holders, NACWOs and others about the health and welfare of the animals must also be nominated. As part of the conditions of the certificate, the holder is responsible for ensuring that the establishment complies with the appropriate Codes of Practice (see paragraph 13.10). They must ensure that proper records are kept about the source, use and eventual disposal of all animals.

***The Home Office Inspectorate***

13.20 The workings of the A(SP)A and the granting of the three types of licence described above is currently administered by the Home Office, rather than by other Government departments, to avoid possible conflicts of interest. Many other departments with responsibility for areas such as human health or the environment may be directly involved in animal research, for example by commissioning or funding research. The Home Office, by contrast, has no such involvement and has therefore been given the task of issuing licences. Its Inspectors are required to have medical or veterinary qualifications and are expected to have experience in scientific research. In 2004, there were 30 Inspectors who assisted in advising the Secretary of State in granting licences and any conditions that should be set. They also provide advice to certificate holders and others with a role under the Act on best practice in laboratory animal welfare. Inspectors make visits to research facilities to ascertain that licence authorities and conditions are being met. They have the right of access to any designated establishment to monitor compliance. At the end of 2003, there were 232 designated establishments in Great Britain. During 2003, the Inspectorate made 3703 visits to departments within establishments in addition to other visits for formal meetings. Over 50 percent of these visits were unannounced.[20]

19 See also footnote 10.

20 Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (London: HMSO).

### *Ethical Review Process*

13.21 Since 1999, each establishment is required to have in place an ERP as a standard condition on all certificates of designation.[21] The purpose of this process is to establish a local framework to ensure that all uses of animals are carefully considered and justified. An ethical review committee should provide independent advice to certificate holders and support to other staff with responsibility for animal welfare.

13.22 The provisions in the *Guidance on the Operation of the A(SP)A 1986* require that the review process includes:

- a named veterinary surgeon;
- representative(s) from among the named animal care and welfare officers;
- representative(s) of the project licence holder(s); and
- representative(s) of the personal licence holder(s).

Facilities are also encouraged, but not required, to involve people who do not use animals, including one or more lay members from outside the institution.

13.23 Functions of the ERP include (where appropriate):

- promoting the development and uptake of Reduction, Replacement and Refinement alternatives to animal use in procedures at the establishment;
- examining the likely costs and benefits of each licence application;
- providing a forum for discussion of issues relating to animal research, and consider how staff could be updated on relevant ethical advice, best practice and relevant legislation;
- undertaking retrospective reviews of licensed projects;
- considering the care and accommodation of animals at the establishment and the humane killing of protected animals;
- reviewing the establishment's managerial systems with respect to animal use;
- advising on staff training and ensuring competence.[22]

The order of this list is often understood to express a hierarchy of importance, and hence the two most important functions of the ERP are considered to be the promotion of the Three Rs and the review of the costs and benefits of research. However, depending on the type of research carried out at specific research facilities, those involved in the ERP may spend more time on other activities. In practice the review of protocols is often the primary focus.

### *Other aspects of the A(SP)A*

Obtaining animals

13.24 Rats, mice and other commonly used laboratory animal species must be obtained from suppliers or breeders that have a certificate of designation and are subject to the same system of controls and inspection as establishments using animals in experiments.

21 See *Guidance on the Operation of the A(SP)A 1986*, Appendix J, available at: http://www.archive.official-documents.co.uk/document/hoc/321/321.htm. Accessed on: 4 May 2005.

22 *Guidance on the Operation of the A(SP)A 1986*, Appendix J, available at: http://www.archive.official-documents.co.uk/document/hoc/321/321.htm. Accessed on: 4 May 2005.

### Genetically modified animals and harmful mutations

13.25 The breeding of animals that are intended for use as disease models, and the breeding of animals for other purposes which are known to cause pain, suffering or distress are classified as scientific procedures. Similarly, the breeding of any GM animal is currently classified as a scientific procedure, because of possible adverse implications for welfare.[23] In 2003, 27 percent of all animal procedures (764,000 in total) involved GM animals, more than treble that of 1995. Two thirds of these were used solely for the purpose of breeding, in order to develop and maintain 'GM lines'; they were not involved in any other procedure or experiment, although some of these animals, once killed, may also have been used to provide tissue for research purposes. The breeding of phenotypically normal animals (i.e. animals that are said to be as 'healthy' as the average wild type of the animal) does not count as a scientific procedure.[24]

### Killing of animals

13.26 Animals that are not used in regulated procedures but killed in designated establishments to obtain tissue samples or because they are surplus to requirements are excluded from the controls of the A(SP)A if they are killed by one of the methods of humane euthanasia listed in Schedule 1 of the Act.[25] Certificate holders must ensure that humane killing is performed by a person who has been trained to use these methods competently.

### Statistics about animal use and information about licences granted

13.27 The Home Office publishes detailed Annual *Statistics* on the numbers and species of animals used in scientific procedures in Great Britain, (see Appendix 2).[26] For reasons related to the licensing process and European reporting requirements, the *Statistics* focus on details about the annual number of procedures started and numbers of animals used for the first time in procedures started that year. Animals used in more than one series of procedures are only counted once (see paragraph 13.17). The *Statistics* do not give any information about the degree of pain and suffering that is actually experienced by animals involved in procedures. This is because the severity banding of procedures, protocols and projects is based on prospective assessments, and because information about severity bands assigned to particular projects relates to the estimated average suffering of all the animals involved (see Box 13.3 and paragraphs 15.25–15.34).

13.28 Section 24 of the A(SP)A makes it an offence for individuals with a function under the Act (i.e. the Minister, his officials and the APC) to disclose any information that they have received in carrying out that function and which they believe to be confidential.[27] Until 2005, practical application of this clause meant that very little information about animal research has been made public. Those wishing for more access argue that the recently implemented provisions of the Freedom of Information Act 2000 (FoI, see Box 13.4) imply that there ought to be more openness.

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23 See paragraph 4.57.

24 However, breeding facilities must have a certificate of designation.

25 Schedule 1 of the A(SP)A sets out 'Appropriate methods of humane killing'. For example, all protected animals may be killed by an overdose of an anaesthetic, using a route and an anaesthetic agent appropriate for the size and species of animal. Dislocation of the neck is permissible for rodents up to 500g, rabbits up to 1kg, and birds up to 3kg.

26 Statistics for Northern Ireland are published separately and not included in the Home Office Statistics for Great Britain. In 2000, 14,124 animals were used in Northern Ireland. See House of Lords Select Committee on Animals in Scientific Procedures (2002) *Animals in Scientific Procedures* (Norwich: HMSO), Chapter 1.

27 See also: Ministerial Statement announcing the outcome of the review of section 24 of the Animals (scientific Procedures Act 1986, 1 July 2004, available at: http://www.homeoffice.gov.uk/docs3/animalproc_wms_section24_040701.pdf. Accessed on: 4 April 2005.

### Box 13.4: The Freedom of Information Act 2000 and its bearing on information about animal research

In 1997, the Government issued the White Paper *Your Right to Know* which led to the Freedom of Information Act 2000 (FoI Act). The FoI Act creates a statutory right of access to information held by public bodies (a definition that includes the Home Office, universities and publicly funded research institutes), provides for a more extensive scheme for making information publicly available and covers a much wider range of public authorities than previous legislation, including: local government, NHS bodies, schools and colleges, universities, the police and other public bodies and offices.* The Act enshrines in law the general right of access to (non-classified) information held by public authorities.† From 1 January 2005 information must be disclosed in response to any such requests made under the FoI Act.

There are also a number of exemptions from the requirement of disclosure, the most relevant ones being for vexatious or repeated requests, where the cost of providing the information would be excessive, information provided in confidence, information relating to the development of government policy, information which, if disclosed, might endanger the health or safety of any individual, information that constitutes personal data under the Data Protection Act and information that, if disclosed, might prejudice commercial interests. These exemptions are disputed by those who argue that they prevent them finding out sufficient information about licence applications and the results of cost-benefit assessments.

The implementation of the new Act with regard to animal research may not be straightforward. Reasons cited by stakeholders include:†‡

- concerns about further increases in the level of bureaucracy already required for complying with the provisions of the A(SP)A;
- concerns about confidentiality of researchers and targeting by those who use unlawful forms of protest;
- concerns about disclosed information being misinterpreted or misrepresented; and
- the Home Office could be required to make decisions about how commercial confidentiality applies to information it holds that relates to commercial companies.

It is difficult to predict the likely scale of information requests that research establishments might receive, and what kind of information may have to be disclosed. It may depend on the type of institution, research being undertaken and how well-known a particular institute is (as it is expected that the more well-known institutions might receive more requests for information). Before the FoI Act entered into force, details of ten project licences had been released by the Home Office to the BUAV, under a Code of Practice that preceded the full FoI Act. The licence applications were anonymised and the institutions involved were not revealed. Details of the purpose of the research, the number and type of animals to be used and the procedures were included.‡∫ In 2005, the Home Office published the first details of project licences granted under the A(SP)A in 'a contribution to greater openness and to contribute to greater public understanding and debate about the use of animals in science and how it is regulated'. Abstracts for several projects, written by licence holders, have so far been published on the Home Office website. The Home Office has announced its future intention to publish details of all new licence applications in this way.** However, those who would like to find out more information regarding the way the cost-benefit assessment is applied consider that these licences abstracts provide insufficient details. We consider the question of openness further in paragraphs 15.35–15.36.

* The FoI Act applies to all recorded information held by public authorities in England, Wales and Northern Ireland and cross-border public authorities. Scotland is covered by a separate act (Freedom of Information (Scotland) Act 2002).

† HMSO (2000) Explanatory Notes to Freedom of Information Act 2000, available at: http://www.hmso.gov.uk/acts/en2000/2000en36.htm. Accessed on: 4 May 2005; Freedom of Information Act 2000 available at: http://www.hmso.gov.uk/acts/acts2000/20000036.htm. Accessed on: 4 May 2005.

‡ LASA (2004) Freedom of Information *The Forum* **1**(3).

∫ Festing S (2004) Freedom of Information Act deadline looms *RDS News* Autumn 2004.

** Home Office (2005) Animal Procedures: Licence abstracts, available at: http://www.homeoffice.gov.uk/comrace/animals/abstracts.html. Accessed on: 4 May 2005.

## Developments in policy

13.29 Since the full implementation of the A(SP)A, a number of changes in the regulatory system have been introduced as a matter of government policy. In the early 1990s, training requirements for all new applicants for personal and project licences were instituted. The Home Office issued a policy statement to make clear that the successful completion of training modules was viewed as necessary in order to meet the requirement in the A(SP)A that licence holders have 'appropriate education and training'.

13.30 In 1997, the Home Office effectively ruled out certain types of animal research: the toxicity testing of cosmetics and (in 1998) their ingredients, alcohol products or tobacco products.[28]

28 House of Lords Select Committee on Animals in Scientific Procedures (2002) *Animals in Scientific Procedures*, Chapter 1; *Guidance on the Operation of the A(SP)A* 1986, Chapter 5, available at: http://www.archive.official-documents.co.uk/document/hoc/321/321.htm. Accessed on: 4 May 2005.

It issued a policy statement to the effect that, in making the cost-benefit assessment, these tests were no longer considered a sufficient benefit to justify any use of animals. In addition, it was announced that, other than in very exceptional circumstances, the use of the great apes would be considered too great a cost to be justified by any possible benefit.[29]

13.31 There have also been other policy developments, concerning controls on the importation of primates,[30] the use of the ascites method to produce monoclonal antibodies (see paragraphs 5.26 and 11.10), the use of certain toxicology procedures (Box 11.2) and the housing and husbandry of certain laboratory species, which have also been introduced by policy statements or the publication of supplementary codes of practice.[31]

## Recent issues of public debate

13.32 The debate in the UK about issues raised by the regulation of animal research is led mainly by a number of national campaigning organisations and some local grass-roots activists who are opposed to animal research (Box 2.4). These groups question whether or not the provisions of the A(SP)A are always interpreted correctly and whether, in practice, they are properly implemented. Some campaigning organisations and activists assert that there is a need for undercover investigations (see Box 2.5). Scientific and medical researchers have responded by creating organisations to communicate their views to the public (see paragraph 2.30 and Box 2.4).

13.33 In general, there has been criticism of the lack of openness about animal research in the UK. Some campaigning groups would like access to applications for project licences to comment on, and where necessary challenge, whether they should be granted (see Box 13.4 and paragraphs 15.35–15.36). Notwithstanding their methodological limitations, surveys of public opinion suggest a widespread lack of trust in the regulation of animal research combined with a lack of understanding about what is done and how it is regulated (paragraph 1.14). The use of primates in research and testing has raised ethical and animal welfare related concerns for many years, and has also been the subject of several campaigns by animal protection organisations. For example, the RSPCA has issued several reports on this issue and initiated campaigns 'to reduce the numbers of primates used and to replace them with more humane alternatives'.[32]

13.34 Further issues are provoked by Section 5 (5) of the A(SP)A which prescribes that licences will only be granted if a non-animal method that could produce the knowledge sought by means of the animal procedure is unavailable. Many campaigning organisations assert that a number of alternatives to using animals in research exist but are not used as widely as they could be in research and testing.[33] Some believe that there are already sufficient alternatives for all research uses of animals to be replaced immediately. Others take the view that existing alternatives are used where possible, but believe that with more effort and funding, it would be possible to develop many new alternatives that could reduce the need to use animals (see paragraphs 11.6–11.30). We return to these issues in Chapter 15.

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29 Animal Procedures Committee (2003) *Review of the cost-benefit assessment in the use of animals in research* (London: Home Office).

30 Where an alternative method is practically available and effective. The use of wild-caught primates has also been abandoned as a matter of policy unless exceptional and specific justification can be established.

31 For example Home Office (1995) *Code of practice for the housing of animals in designated breeding and supplying establishments*, available at: http://www.homeoffice.gov.uk/docs/cop_hcasp.html. Accessed on: 4 May 2005.

32 RSPCA (2005) Primates, available at: http://www.rspca.org.uk/servlet/Satellite?pagename=RSPCACampaigns/Primates/PrimatesHomepage. Accessed on: 4 May 2005.

33 For example, Dr Hadwen Trust, available at: http://www.crueltyfreeshop.com/drhadwen/faq.htm. Accessed on 6 May 2005.

## International regulation

13.35 The basic principles that underlie the regulation of animal research are very similar in all countries in which animals have legal protection. Regulations specify the conditions under which animals may be used and seek to ensure that harms are minimised as far as possible. They are usually implemented through review of proposed research projects, applying the Three Rs where possible and assessment of the general standards of laboratory animal housing and husbandry.

13.36 However, countries differ in the complexity and detail of regulations, and the manner and strictness with which they are implemented and enforced. Some countries do not have national regulatory systems and use guidelines or policies developed by individual institutions. For example, Canada relies on a well-developed voluntary system of self-regulation based upon protocol review by institutional Animal Care Committees, which operate according to guidelines set out by the Canadian Council on Animal Care.[34]

13.37 The system of project review by an institutional committee is the most common method of self-regulation in most countries. Committees typically involve scientists with experience in the field and veterinary staff. In some cases, these committees have a broader membership which includes animal technicians, non-technical staff of the institution, external lay members or representatives with an interest in animal welfare.

13.38 In many countries, the detailed operation of these committees is controlled by agencies that fund research. The USA has an extensive system of Institutional Animal Care and Use Committees (IACUCs), created by the Animal Welfare Act and its regulations.[35] The Act covers the use of warm-blooded animals in research, but excludes rats, mice and birds. The IACUCs operate according to the more detailed policies and guidance published by the National Institutes of Health.[36] Australia uses a similar system of Animal Ethics Committees, created under state legislation, but operating in accordance with the code of practice produced by the National Health and Medical Research Council.[37]

13.39 Within Europe, there are two, almost identical, legal instruments. They are the Council of Europe *Convention for the protection of vertebrate animals used for experimental and other scientific purposes* (ETS 123, 1986), and the EU *Directive EEC 86/609 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes*. The legal status of these instruments differs. Member States of the Council of Europe can decide whether or not to ratify the Convention by implementing it in their national legislation. By contrast, Member States of the EU are legally obliged to implement the goals set out in the Directive. All have transposed the Directive in their national or regional legislation, although the European Commission has referred several countries to the European Court of Justice to ensure that their legislation is fully in accordance with the Directive.

34 See *Canadian Council on Animal Care*, available at http://www.ccac.ca/. Accessed on: 4 May 2005.

35 US Department of Agriculture *Animal Welfare Act and Regulations*, available at: http://www.nal.usda.gov/awic/legislat/usdaleg1.htm. Accessed on: 4 Apr 2005.

36 See the Report of House of Lords Select Committee on Animals in Scientific Procedures (2002) *Animals in Scientific Procedures* (Norwich: TSO) for a description of the US system of regulating animal research. In the USA there is no legal obligation to report the numbers of mice and rats used in experiments. The system of regulation means that privately funded companies that use only rats, mice and birds are not subject to the same federal regulations or inspections as those that apply for researchers and institutions that receive federal funds.

37 National Health and Medical Research Council (2004) Australian code of practice for the care and use of animals for scientific purposes, 7th Edition, available at: http://www.nhmrc.gov.au/publications/pdf/ea16.pdf. Accessed on: 4 May 2005.

13.40 The main current provisions of the EU Directive are that:

- establishments conducting animal experiments must be registered with the authorities and maintain the housing and husbandry of the animals according to a standard set out in an annex to the Directive;
- experiments must only be conducted by, or under the direct responsibility of, a competent, authorised person, who should have appropriate education and training;
- animals cannot be used if another, scientifically satisfactory, method is available;
- experiments must be designed to use the minimum number of animals, the species with the lowest neurophysiological sensitivity and to cause the least pain, suffering, distress or lasting harm, compatible with the purpose of the experiment;
- wild-caught animals are not used unless necessary for the experiment;
- the experiments to be performed, or the details of the individuals who will perform them, must be notified in advance to the authorities;
- experiments that may cause severe pain that is likely to be prolonged must be justified in advance and authorised by the authorities;
- statistical information on the numbers and types of experiments conducted must be collected by the authorities; and
- breeding and supplying establishments must be registered and comply with the same standards as experimental establishments.

13.41 There is a significant variation in the national systems for regulating animal research introduced under the Directive. Member States are permitted to adopt stricter measures if they wish. Several countries have done so, including the UK. The UK system is widely considered to be the most comprehensive and detailed in the EU (and throughout the world). Nevertheless, there are some countries that regulate specific aspects of animal research that are not regulated in the UK. For example, training requirements are more detailed in The Netherlands, and provisions for freedom of information are more liberal in Sweden.

13.42 Most EU countries originally implemented the Directive with 'external' regulation, which means that authorisations for research projects are given by national or local government officials. Some countries opted for a system in which local or regional animal ethics committees authorise research involving animals. None of the EU countries have implemented systems of self-regulation.

13.43 The system of regulation in most Member States uses either one or two licences. The main licence usually covers the research or testing activities of an institution and serves as the registration of the establishment and the licence for the research to be conducted. Other countries use separate licences for the institution and the projects, which may include details of the personnel who will carry out the research. For example, in France the personal licence is akin to the project licence in the UK; applicants submit an application that includes broad details of the intended project.[38]

13.44 To fulfil the requirement in the Directive for 'verifying that the provisions of this Directive are properly carried out', most Member States have established a system of inspection of establishments that conduct animal experiments. This function is usually added to the role of local veterinary inspectors, whose primary role is to inspect agricultural use of animals. Very few countries have statutory systems of inspection dedicated exclusively to animal research. In

38 House of Lords Select Committee on Animals in Scientific Procedures (2002) *Animals in Scientific Procedures* (Norwich: TSO), Chapter 1.

The Netherlands there are three inspectors for the 600,000 animals used annually (see paragraph 13.20). In the USA, only institutions that conduct research involving certain classes of animal covered by the Animal Welfare Act are subject to inspections from the US Department of Agriculture. Additional levels of inspection operate for institutions that receive federal funds. The non-governmental Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) also carries out inspections of accredited institutions. Accreditation is voluntary but includes most large companies and major universities as accreditation is an important factor for securing contracts and funding.[39]

13.45 Since the Directive was adopted in 1986, there has been a trend towards increased and more detailed regulation in many Member States.

- France, The Netherlands and some parts of Spain have added a system of local animal ethics committees to their previously existing systems of control.
- Austria, The Netherlands, Sweden and the UK have abandoned the use of great apes in scientific procedures, although they had not been used in the UK and Sweden for some years.[40] With the voluntary retirement of a colony used in vaccine development in Austria, no great apes were used in the EU in 2002, the last year for which statistics are available.[41]
- The Netherlands and the UK have ceased using animals for testing cosmetics or cosmetic ingredients. Germany and Austria have introduced partial bans, permitted testing under some circumstances. More recently, a ban on the use of animals within the EU for the testing of cosmetics has been passed and is due to come into force in 2009 (and sales within the EU will not be allowed after 2013). However, there are certain exceptions for particular types of test and the EU Directive on cosmetics testing on animals is currently under legal challenge from the French Government.[42]
- The Netherlands and the UK have banned the acute oral $LD_{50}$ test (see paragraph 9.14 and Box 11.2), with very limited exemptions.

13.46 Under the Council of Europe's Convention ETS 123 there are periodic meetings of representatives of the Member States and relevant non-governmental organisations to 'examine the application of this Convention, and the advisability of revising it or extending any of its provisions'. In 1997, the revision of Appendix A to the Convention, which gives guidelines for the accommodation and care of laboratory animals, was agreed. The revised Appendix A will include details about the husbandry and housing of all the principal laboratory animal species. It is expected that the Council of Europe will adopt the new Appendix in 2005. Since the EU ratified the Convention, Appendix A will be adopted as a revised Annex II to Directive EEC 86/609.

13.47 In 2001 the European Commission proposed that Directive EEC 86/609 should itself be revised. This process started in 2003 when the Commission formed four Technical Expert Working Groups (TEWGs) to offer advice on how the existing Directive could be improved. Discussions are currently in progress but it is likely that a revised Directive will not be adopted for several years. The provisions of the new Directive will be transposed into national legislation once the revisions have been agreed.

39 *Ibid*. Chapter 1.

40 Great apes have not been used for research in the UK since the passing of the A(SP)A in 1986. See House of Lords Select Committee on Animals in Scientific Procedures (2002) *Animals in Scientific Procedures* (Norwich: TSO), Chapter 1.

41 European Commission (2005) *Fourth Report on the Statistics on the number of animals used for experimental and other scientific purposes in the Member States of the European Union* (Brussels: EC).

42 Directive EC 2003/15 amending Council Directive EEC 76/768 on the approximation of the laws of the Member States relating to cosmetic products.

## Regulations requiring the use of animals

13.48 So far, we have concentrated on regulation that authorises and prescribes the ways in which animals can be used in research, seeking to minimise possible harm. As we have said (see paragraphs 8.22 and 9.4), animal research is also undertaken because regulations at both the national and international levels stipulate that medicines, vaccines and chemicals for use in agriculture, industry, food and household products must be tested for efficacy and safety. Some regulations require that animals must be used, whereas others merely require that tests must be undertaken according to best practice, which is often interpreted as requiring the use of animals. Companies and institutions within countries such as the UK, which are members of many different international organisations and operate in international markets, are also subject to overlapping legislation and guidelines.

### *Testing of medicines*

13.49 In the UK, new medicines must meet the requirements of the Medicines Act 1968 in order to be licensed. The Act states that a medicine must demonstrate that it is safe, effective and of high quality and this is usually interpreted as requiring testing on animals.[43] EU legislation, particularly Directive EC 2001/83 on the Community code relating to medicinal products for human use, now takes precedence over the Medicines Act, which has been amended several times to align with new requirements. The Directive requires that all new prescription medicines are studied in animals before they are tested in humans. It states that before a new medicinal product can be marketed in the EU, the producer shall obtain authorisation by the appropriate competent authority (either the national regulatory agency or the EMEA). Article 8 (3) stipulates that an application to one of these agencies shall include: 'Results of: physico-chemical, biological or microbiological tests, toxicological and pharmacological tests, [and] clinical trials'. The exact requirements, standards and protocols for both animal and non-animal tests are described in detail. For example, single-dose toxicity shall be assessed by the following protocol:

> 'The acute toxicity test must be carried out in two or more mammalian species of known strain unless a single species can be justified. At least two different routes of administration shall normally be used…'[44]

13.50 In other countries, medicines are licensed through equivalent regulatory authorities such as the Food and Drug Administration (FDA) in the US and the Ministry of Health, Labour and Welfare in Japan. The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) coordinates the pharmaceutical regulatory authorities of Europe, Japan and the USA (see paragraph 12.8). It aims to harmonise guidelines on quality, safety and efficacy in its member countries. Certain of its safety guidelines specify that animal research should be performed.[45]

### *Testing of chemicals*

13.51 Primary UK legislation requiring the testing of chemicals includes the following: the Health and Safety at Work Act 1974, the Consumer Protection Act 1987 and the Food Safety Act 1990. These acts mostly implement the provisions of corresponding EU directives. The OECD

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43 See *Animals in Medicines Research Information Centre*, available at: http://www.abpi.org.uk/amric/basic5.asp. Accessed on 5 May 2005.

44 EU Directive EC 2001/83, Annex 1, Part 3 *Performance of Tests: Toxicity*.

45 See *The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)*: Safety Guidelines, available at: http://www.ich.org/UrlGrpServer.jser?@_ID=276&@_TEMPLATE=254. Accessed on: 5 May 2005.

has harmonised the testing of new chemical compounds across member countries, including the UK, USA, Japan, France and Germany. Certain OECD testing guidelines require the use of animals.[46] These are a collection of methods developed by OECD member countries for identifying the hazards of chemical substances (see paragraphs 9.5 and 12.8).

***Differences in international test guidelines***

13.52 There is some variation in the data and methods that different national regulatory authorities are willing to accept, when assessing, for example, the safety or efficacy of new medicinal or agrochemical products. Although organisations such as ICH and OECD aim to achieve a certain degree of harmonisation, it is often the case that a single chemical that is marketed in a number of countries might need to be tested several times for toxic effects, in order to satisfy national standards. For example, during the Working Party's fact finding meeting with experts from the Home Office, reference was made to a licence that had been granted for vaccine trials on primates involving procedures of substantial severity. This type of animal use typically involves the immunisation of animals with a candidate vaccine, and subsequent exposure to the infective organism. A range of different doses of the vaccine are then administered, to assess its efficacy and safety. The test requirements and methods are generally set at European or higher supra-national levels and usually require that the test be continued until it becomes clear that the animals have not survived the disease. The Home Office took the view that trials should be stopped at an earlier stage if the scientific objective can be achieved. At the time of writing, the matter was being discussed with relevant stakeholders and regulators to encourage the development and adoption of such measures, and to identify earlier endpoints for studies.[47] However, different conceptions of what qualifies as sufficient scientific evidence for the safety and efficacy of new chemicals, different frameworks for liability and compensation, as well as general political disagreements between nations, all contribute to complications in the harmonisation of laws and guidelines on animal testing. We continue the discussion on the international context of animal research in paragraphs 15.84–15.87.

## Summary

13.53 We have described important aspects of the national and international regulatory framework governing research involving animals. In doing so, we have focused on legislation for the protection of animals, briefly summarised regulation relating to the requirement of animal tests, and highlighted difficulties in the harmonisation of different national policies. We described the historical background to the A(SP)A, its principal provisions, and the three types of licence that govern all animal research in the UK: personal licences, project licences and certificates of designation. In carrying out the cost-benefit assessment, which is fundamental to the A(SP)A, the primary responsibility lies with the researchers planning a new project. In addition, a number of other people and processes are involved, and it would be fallacious to assume that only the inspectors of the Home Office are responsible for carrying out this assessment. The Home Office publishes annual statistics about the numbers of animals used in research. These contain information about prospectively assigned severity banding of granted project licenses but `do not provide

46 See OECD (1993) *Chemicals Testing: OECD Guidelines for the Testing of Chemicals – Sections 1–5*, available at: http://www.oecd.org/document/22/0,2340,en_2649_34377_1916054_1_1_1_1,00.html. Accessed on: 4 Apr 2005.

47 This is consistent with the current general approach of the Home Office, which requests that a trial should be stopped if signs occur that reliably predict the death of the animal. If such signs manifest themselves, the animal is to be humanely killed, instead of dying from the disease, see Home Office (2003) *Animals (Scientific Procedures) Act 1986: Guidance on the Conduct of Regulatory Toxicology and Safety Evaluation Studies*, revised June 2003, available at: http://www.homeoffice.gov.uk/docs2/regtoxicologydraftrevision4_03.html. Accessed on: 5 May 2005.

details about the levels of pain, suffering and distress actually experienced by animals. The ERP is critically important. Three of its most significant functions are to act as a forum for discussion of the Three Rs, to consider ethical and regulatory issues raised by animal research and to undertake an initial cost-benefit assessment before a licence application is passed to the institute's certificate holder.

13.54 As has become clear during the discussions of members of the Working Party and also from responses to our Consultation, views differ on whether the provisions of the A(SP)A are sufficient in scope and detail; whether they are always interpreted correctly; and whether, in its practical application, the legal requirements are always implemented effectively. For example, respondents to the Consultation made the following observations:

> 'I'm not sure that present regulations are appropriate. For one thing how can researchers tell if there will be welfare problems in advance?'
> *Anonymous*

> 'Current provisions for the assessment of welfare of animals are rigorous and of high quality, but must be continuously revised and improved as our knowledge and understanding increases… Assessments of welfare should be conducted before, during and after a project.'
> *Biosciences Federation*

> 'Although inspection is important, it is the culture of care at a particular establishment which is paramount. In this regard, the Ethical Review Process mandated by A(SP)A is I believe unique to UK legislation. The Home Office Inspectors play a valuable role in education and sharing of best practice in this activity.'
> *Anonymous*

> 'Legal protection for GM animals is inadequate and changes in the law are required in order to afford them due consideration. This is, not least, because their use, certainly on its current scale, was not foreseen when that legislation was introduced.'
> *Animal Aid*

> 'The current licensing system proscribes everything which is not specifically permitted on an individual project basis, rather than legislating what may and may not be done by everybody in order to maintain standards of welfare. This has generated a vast bureaucracy which undoubtedly impedes the progress of science.'
> *Dr R M Ridley and Dr H F Baker*

> 'Significant tightening of regulation would make either research more difficult, increase costs and delay patient benefits or move research off shore to less detailed regulatory climates, at a significant cost to the UK's science base as well as to the welfare of the animals involved.'
> *Genetic Interest Group*

13.55 The Working Party's conclusions and recommendations with regard to regulatory aspects of animal research are presented in Chapter 15 (see paragraphs 15.53–15.56 and 15.84–15.87). So far we have reviewed the wide scope of costs and benefits arising from the uses of animals in different areas (Chapters 4–9), as well as the current state and potential of the Three Rs (Chapters 11 and 12) and the regulatory framework. We now consider how these findings should be viewed from an ethical perspective.

# Chapter 14

## Discussion of ethical issues

# Discussion of ethical issues

## Introduction

14.1 In this chapter we resume the discussion about ethical issues raised by research involving animals. We also consider basic questions about how public policy should be shaped in this area where there is widespread disagreement among members of the UK population. In Chapter 3 we argued that the ethical question is best thought of not simply in terms of the relative moral status of humans and animals, but by consideration of two questions: first, what features of human and animals make them objects of moral concern; and second, how should those features be taken into account in moral reasoning: through weighing of factors or through the generation of absolute prohibitions?

14.2 We suggested that there are five features that have the potential to give rise to moral concern: sentience; higher cognitive capacities; capability for flourishing; sociability; and possession of a life (paragraphs 3.27–3.50). The last of these was the most controversial. We also explored how to consider these features in moral reasoning. A consequentialist view weighs all costs against all benefits (paragraphs 3.52–3.55). A deontological view lays down particular prohibitions (paragraphs 3.56–3.57). A hybrid view contains some prohibitions and some weighing (paragraphs 3.58–3.62). We also concluded that the ethical positions that coincide with the current UK regulations are hybrid (paragraph 3.58). It appears that, in practice, the positions of most people, except perhaps those of animal protection groups, are hybrid too, allowing some weighing of factors, and accepting absolute prohibitions in other areas.[1]

14.3 If we accept that most views are hybrid, then we can see that the debate comes down to disagreement on two questions: first, what are the absolute constraints? and secondly, how do we weigh different morally relevant factors within the permitted area? To answer these questions, we will always need to consider at least five questions:

i) what are the goals of research?

ii) what is the probability of success?

iii) which animals are to be used?

iv) what effect will there be on the animals used in the experiment?

v) are there any alternatives?

14.4 To bring the basic moral issues into sharp focus, we consider first, as a purely hypothetical example, an abstraction that might be considered by many people as a relatively uncontroversial type of animal experiment. We assume that the goal of the research is the saving of human life through the eradication of a widespread painful and debilitating childhood disease; that there is a high probability of success; that the experiments can be conducted on a small number of mice; that the animals will suffer only mild discomfort, although they will have shortened lives; and that no acceptable alternatives will be available in the foreseeable future however much effort we expend. What objections could there be, if all these conditions are met?

14.5 In considering the example it is important to be aware that it has been drawn up in such a way that the total benefits of the experiment (to humans) are in some sense greater than

[1] Even some of those opposed in general to animal research may allow that some research involving animals is permissible; for example non-harmful observation of animals in their natural habitat for the purpose of conservation, and possibly mildly harmful research that entails tagging or ringing of animals.

the total costs (to the animals). However, it is a further step towards the conclusion that the presence of a positive total of benefits justifies the experiment ethically. There are at least two reasons why such a justification might be rejected:

- First, a number of mice will die. Some people argue that the value of any life is such that it would be wrong deliberately to take a life for any purpose, even for the saving of a greater number of human lives. This can be called the view that *life has absolute value*. Other people might assert that although the taking of a life has no absolute value, it still has *intrinsic value* in the sense that it would be wrong deliberately to take a life for any purpose without careful justification.
- Secondly, whether or not there is a value to life, it is clear that mice are being used for the sake of human beings. Even if one takes the view that human life is much more important than the comfort and lives of laboratory mice, and that the weighing of relevant factors clearly supports the experiment, nevertheless the laboratory animals suffer costs and do not accrue any benefits, while humans receive all the benefits. This problematic distribution of costs and benefits gives rise to the objection from *forced consequentialist sacrifice*. It is a notorious problem with any consequentialism that the costs may fall in one place and the benefits arise in another. In some cases, for example within a political society or an economic community, this asymmetry may even out over time so that those who suffer today may gain tomorrow, but clearly this is not the case with the individual animals used in laboratory experiments. Similarly, it is irrelevant to point out that sometimes *animals* benefit from animal research, for the animals which benefit are not the ones on which the experiments are conducted.

14.6 The importance of the last paragraph is that independently of morally relevant features such as sentience, higher cognitive capacities, capability for flourishing and sociability, the acceptance of even relatively mild experiments for great benefit depends on the acceptance of two vital moral assumptions: that the life of laboratory animals such as mice does not have absolute value; and that consequentialist sacrifice is acceptable. There is no consensus within the Working Party as to whether these assumptions are morally acceptable. But we do agree with the conditional: harmful research involving animals must be morally unacceptable if animal life is seen as having absolute value, or if forced consequentialist sacrifice is always seen as wrong.

14.7 There is, however, still much room for disagreement among those who deny that animal lives have absolute value and who accept at least some forced consequentialist sacrifice. Nonetheless, the Working Party has not been able to agree on a common ethical stance with regard to the conditions that have to be met for animal research to be justified. Instead, we offer below an outline of four possible positions that can be taken. These views should be understood as marking positions on a *continuum*.

14.8 As will become clear, members differ not only in their positions on what forms of animal research can be morally justified, but also in their views about the status of morality itself. That is, whether it is universal, absolute and discernible by reason; whether it is largely conventional, socially relative and invented by human beings, to be discovered by sociological research; or whether some other philosophical theory of morality is correct (see paragraphs 3.4–3.7). Consequently, in the following we do not provide a statement of the Working Party's collective moral view, substantive or philosophical, which would be based on one single moral theory. Rather we aim to achieve a number of different goals, as follows:

- Our primary aim is to provide a clearer understanding of the range of moral views held on issues raised by animal research, both within the Working Party and outside, and of

the reasons that people hold them. Too often the debate about animal research is presented in a very simplified and polarised manner, differentiating between 'those opposed' and 'those in favour'. Our own discussions, and our analysis of responses to the Consultation, have indicated that such perceptions are overly simplistic and unhelpful in furthering fruitful debate.

- From a philosophical perspective, consideration of the range of different views is useful because they illustrate the complex structure of ethical justification. Like other areas of controversy in bioethics, the topic of research involving animals challenges us to test, and if necessary revise, our ethical framework in view of our considered judgements about specific areas of research (paragraph 3.7).
- Lastly, and perhaps most importantly, we also aim to clarify more precisely the scope of agreement and disagreement between different views, and the sources of disagreement. Such an exercise is helpful in reducing disagreement as far as possible, in order to identify an ethically based public policy, which, while it may not entirely accord with any particular moral framework, may be seen as reflecting a broad agreement that provides for the best accommodation of views that can be achieved under current conditions.

14.9 Before we present an outline of a range of ethical views, we need to make one further important observation. We have said that the Working Party does not take a view on the status of morality itself. Thus, it might be thought that the Working Party was content to agree with the following two statements.

- 'All claims that are given a moral justification are equally valid, and hence all of the four views presented below are equally valid. Morality comes down to a matter of "picking and choosing".'
- 'If there were a country in which all inhabitants agreed that there was nothing wrong with causing pain, suffering, distress or death to animals, then the matter would be entirely up to those people and they would not deserve moral criticism.'

14.10 The Working Party does not agree with either of these statements. With regard to the first, all members of the Working Party associate themselves with one (or more, depending on the context) of the views that we set out below. In holding their particular view, they are willing to defend their reasons and justifications for coming to particular conclusions, and they challenge others to do the same, in a calm and civilised manner. All members strive to achieve coherence between their considered judgments or intuitions about specific cases of animal research, the relationship to judgments about similar cases, and the principles, rules and theoretical considerations that govern them. Discussion of conflicts between these views provides welcome opportunity to engage in this process. The reader is invited to judge whether one or other of the positions is superior to others. However, in presenting them, we are clear there is no such thing as an 'off-the-shelf' morality. Moral frameworks are not acquired and maintained in a simple 'pick-and-choose' fashion. Rather, they require continuous scrutiny and justification.

14.11 With regard to the question of whether or not people of a country that showed no concern for any animals deserved moral criticism, all members of the Working Party agree that this would be so. No member takes the view that complete disregard for the five morally relevant features – sentience, higher cognitive capacities, capability for flourishing, sociability and the value of life – can be ethically justified. In this sense all members agree that the purposeless infliction of pain, suffering, distress or death to animals is a universal moral wrong. However, we disagree about the reasons for reaching this conclusion (paragraphs 3.7 and 14.8).

14.12 We consider the relation of ethical theory to public policy in more detail below (paragraph 14.53-14.63) and now turn to the four possible stances on animal research. Presenting four views rather than one may be disappointing to some. Nevertheless we believe that it is the most appropriate way of taking the complexity of the debate seriously, and providing guidance to those wishing to engage in thorough ethical analysis.

## Summary: four views on the ethics of animal research

***The 'anything goes' view***

From this viewpoint, if humans see value in research involving animals, then it requires no further ethical justification. It is overly regulated and the primary reasons for implementing the Three Rs are economic or scientific necessity. This position marks one end of the spectrum,[2] and is not held by any members of the Working Party.

***The 'on balance justification' view***

Here it is argued that although research involving animals has costs to animals, which must be taken seriously in moral reasoning, the benefits to human beings very often outweigh those costs in moral terms. Hence it is argued that in accepting research involving animals one acts with full moral justification, while accepting that every reasonable step must be taken to reduce the costs that fall on animals, and that some forms of research are not justified.

***The 'moral dilemma' view***

From this viewpoint it is argued that most forms of research involving animals pose moral dilemmas: according to the current scientific approach the use of animals is necessary to comply with the moral imperative to cure human disease and to save human lives. This also means that animals are treated in ways which are morally wrong. Accordingly, however one decides to act, one acts wrongly, either by neglecting human health or by harming animals. Both alternatives cause severe regret to moral agents, and there is no justification either in principle or in general for conducting, or neglecting to conduct, research involving animals. In order to prevent further dilemmas, the implementation of the Three Rs, particularly of Replacements, must be a priority.

***The 'abolitionist' view***

According to this view, humans experiment on animals not because it is right but because they can. Since any research that causes pain, suffering and distress is wrong, there is no moral justification for harmful research on sentient animals that is not to the benefit of the

2 More accurately, the spectrum might be constructed as follows: (i) humans are *morally required* to carry out any kind of animal research they deem desirable; (ii) humans are *morally permitted* to carry out (specific types of) animal research; (iii) humans are *morally prohibited* to carry out any type of animal research. The 'anything goes' view falls primarily in category (i), the 'on balance justification' and the 'moral dilemma' views belong primarily in (ii) and the 'abolitionist' view in category (iii). The spectrum presented here does not begin with what might be conceived of as the most 'liberal' view, since the 'anything goes' view is characterised by stating that 'research requires no further ethical justification', and it is therefore relatively close to category (ii). The reason for this structure is that the Working Party found it difficult to consider in isolation a view according to which humans were required to carry out any type of animal research. While all members agreed that there were well-grounded moral reasons that require humans to undertake *research*, it is less straightforward to conceive of good arguments that would support the argument that humans are required to carry out any research specifically requiring the use of *animals*. Thus, while such a position is conceptually possible, in practice it is difficult to construe. Moreover, arguments according to which humans are morally required to undertake *specific types* of animal research are found in the 'anything goes', the 'on balance justification' and the 'moral dilemma' views. Therefore, although the logical (liberal) end of the spectrum is not represented here, different versions of the more practical argument according to which humans are morally required to use animals in certain circumstances *are*. We hope that the discussion of the tension between these moral requirements, and the concerns that may arise in deliberations about their pursuit, are useful.

animal concerned. The greater the impact on the animal's welfare, the more objectionable the research. This is seen as valid irrespective of any possible scientific, medical or other benefit. Since humans should not act in morally objectionable ways, every effort must be made to bring an end to all animal research as soon as possible.

A view that is related to the 'abolitionist' view, but which is not considered in the same detail as the other four views above, can be called the 'weakness of morality' view. Proponents of this perspective agree with the abolitionists that from a moral point of view it is simply wrong to use animals for any human purposes that compromise their welfare in ways that are not in their interests. Despite this belief, holders of this view find that they are not motivated to act on it, for example by campaigning for the abolition of all research involving sentient animals.

## Discussion: four views on animal research

14.13 We now consider these four positions in more detail. Before doing so, it is worth referring to an issue briefly raised in Chapter 3: the relevance of the solidaristic preference that many human beings have for each other over animals. We noted that from one viewpoint this was considered 'speciesism', analogous to racism or sexism, while from another this preference is fully justified (see paragraph 2.17 and Box 3.4). Indeed, from some views such preferences are themselves the basis of morality. This reasoning expresses itself in a number of ways. It can draw on the biological or evolutionary order of humans and other animals, or on philosophical or religious frameworks. For example, the higher status of humans vis-à-vis animals can be based on the Judeo-Christian tradition, in which a moral difference between human beings and animals may be presumed by the order of creation in Genesis.[3]

14.14 As we will see the 'abolitionist' view considers that whatever moral strength such solidaristic preferences have, universalistic morality silences them. The weakness of morality view agrees that this ought to be the case but denies that morality can, in practice, overturn such a powerful psychological drive. The 'moral dilemma' view, at least in one version, accepts both the universalistic argument of the abolitionists, while also accepting that solidaristic reasoning has a moral foundation. This tension can be what causes the dilemma. Finally those holding the 'on balance justification' or the 'anything goes' views usually believe that species solidarity outweighs universalistic morality. Consequently we see that the question of the nature and value of human solidaristic preferences for each other is, morally speaking, right at the heart of this debate. Some view such preferences as immoral, while others see them as absolutely at the heart of morality. We cannot settle this question, although we can acknowledge its powerful psychological grip on many humans and its crucial role in the debate.

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3 The Biblical justification of the superiority of humans over animals was based on the claim that God had created humans, uniquely, in his own image, giving them the highest status among living beings (see Book of Genesis (1:28) (2001) *The Holy Bible, English Standard Version* (Wheaton, IL: Crossway Bibles): 'And God said to them [man], "Be fruitful and multiply and fill the earth and subdue it and have dominion over the fish of the sea and over the birds of the heavens and over every living thing that moves on the earth."') However, as noted above (paragraph 3.21) this view should not be taken to mean that humans are free to treat animals in any way they please. In fact, it may well enjoin them to maximise animal welfare as far as possible. This interpretation would not only be compatible with Christianity, but also, for example, with Judaism and Islam. Religious arguments can support a range of views which we discuss in the remainder of this Chapter, especially the 'on balance justification' view (paragraphs 14.21-14.27) and the 'moral dilemma' view (paragraphs 14.28-14.40). While we have not considered the special perspective of different religions on the question of animal research in this Chapter, we are clear that for many people it would be wrong to suggest that a strict distinction between religious, ethical and public policy perspectives can be made. We therefore present the outline of the four views that follow on the understanding that religious arguments can be of equal status and relevance in the justification of specific uses of animals, as those grounded in secular ethical theory. For a further discussion of religious perspectives on the use of animals see Linzay A (1995) *Animal Theology* (Illinois: University of Illinois Press).

14.15 With this background in mind we now address for each view four questions: (i) what is the justification for using animals in research? (ii) how does the justification relate to the treatment of animals in other contexts? (iii) what is the value of research? (iv) what is the role of the Three Rs?

***The 'anything goes' view***

Justification for using animals in research

14.16 As we have said, all members of the Working Party agree that research involving animals requires ethical justification. People holding different views might refer to the philosophers Malebranche and Descartes, who established a dualistic conception of mind and body that only applied to humans, arguing that animals lacked relevant cognitive capacities. According to Descartes, animals were not sentient or capable of suffering pain or distress (paragraphs 3.30 and 4.4). Based on a somewhat different assumption, in the 1960s proponents of a philosophical approach called behaviourism came to similar sceptical conclusions about mental capacities of animals. Although this approach still features in some journalistic contributions[4] to the ethical debate about animal research, it has little currency in contemporary academic discussion.

Using animals in research and in other contexts

14.17 We have observed that a useful way of addressing ethical issues raised by harmful uses of animals is to identify morally relevant features, and to assess how these features should be considered in moral reasoning. The Cartesian and similar approaches simply focus on one of these features (higher cognitive capacities), and consider that this justifies categorising all animals as outside of the moral community (see Box 3.1). Nonetheless, even such radical approaches which deny animals any moral status need not allow any wanton cruelty towards them, as it can be argued that humans who are cruel to animals are more likely to be cruel to humans (the Kantian argument). Thus, the most liberal framework conceivable[5] with regard to the use of animals in research could still prohibit some treatments of animals in other contexts; for example, some forms of hunting, or pest control without regard to the way in which animals were killed.

The value of research

14.18 Although the 'anything goes' view is hardly a feature of the current debate, some people, for example those affected by severe diseases such as cystic fibrosis, Huntington's or Parkinson's might argue for a very low threshold in specific cases. Some patients waiting for new or improved therapeutic interventions could take the view that the interests of animals used for medical research should be given far less consideration than their own, regardless of whether experiments are at an early stage in basic research, for example, to understand disease processes, or at more advanced stages, such as to test a new therapeutic intervention. To others, such an argument based on need appears unjustified, and they point out that there are also a great number of patients who disagree and prefer not to cause animals suffering in their name.

14.19 Research on diseases such as cystic fibrosis or neurodegenerative disorders involves animals at different levels of neurological and behavioural development, ranging from mice to

4 Guldberg H (2004) Why Humans are Superior to Apes Spiked 24 February, available at: http://www.spiked-online.com/Printable/0000000CA40E.htm. Accessed on 6 May 2005.

5 See footnote 2.

primates. It will therefore infringe on the animal's morally relevant properties (sentience, higher cognitive capacities, capacity to flourish, sociability and possession of a life) to varying degrees. We observed above that the question of whether or not other animals, and particularly primates, have higher cognitive capacities that can be compared in a meaningful way to those of humans is the subject of continuing research paragraphs 3.30, 4.4 and 4.27). No member of the Working Party is persuaded that a person's experience of suffering can justify the unlimited imposition of pain or suffering by research animals, regardless of whether they are mice or primates. However, we agree that patients' views should be fully considered in deliberations about the permissibility of animal research alongside other voices in the debate.

The role of the Three Rs

14.20 While views on the Three Rs may differ among those sympathetic to the 'anything goes' view, many proponents may view them with scepticism. Although Refinement will be relevant to all those who do not deny the capacity of suffering to animals, in general the Three Rs are likely to be of interest primarily insofar as they contribute to more economic and effective scientific progress, for example where Refinements are necessary so as not to compromise the scientific validity of results from animal research.[6]

***The 'on balance justification' view***

Justification for using animals in research

14.21 In Chapter 3 we referred to a number of normative ethical theories in our attempt to determine the appropriate consideration of morally relevant features of animals. These theories include deontological, consequentialist, utilitarian and virtue-ethics-based approaches and all may be used to justify some animal research. Many approaches have as their basis the argument that there is a moral primacy of humans over animals. There are also arguments based on the biological or evolutionary order of humans and other animals (paragraphs 3.20–3.26) as well as religious frameworks or other notions of solidaristic preference (paragraph 14.14).

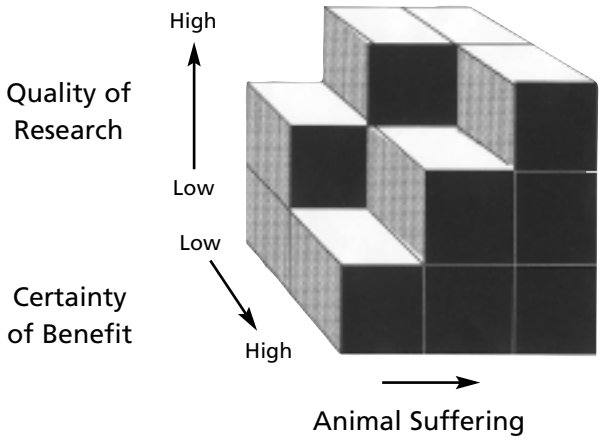
14.22 Unlike proponents of the 'anything goes' view, supporters of this view acknowledge that research entails costs to animals, which must be taken seriously in moral reasoning. However, very often the benefits to human beings are seen to morally outweigh the costs to animals. Proponents point to the statistics about the level of pain, suffering and distress experienced by animals in research and note that, for example, 39 percent of project licences in force at the end of 2003 were classified as mild (56 percent as moderate, see Appendix 2). They take the Statistics to be broadly representative of animal suffering, view the levels as acceptable, and emphasise that the law requires that experiments must be designed to use the minimum number of animals, drawn from the species with the lowest neurophysiological sensitivity. They further argue that the welfare implications are experienced in far less negative ways by animals than by humans (paragraphs 3.29). Hence, in view of the important goals of many research programmes using animals, and the lack of alternatives, they argue that in accepting animal research they act with full moral justification. Nonetheless they can also hold that every reasonable step must be taken to reduce the costs that fall on animals, and that some forms of research are not justified.

6 Derbyshire S (2001) Animal Research: A scientist's defence *Spiked* 29 March, available at: http://www.spiked-online.com/Printable/000000005547.htm. Accessed on 6 May 2005.

Using animals in research and in other contexts

14.23 On most versions of the 'on balance justification' view, it would appear that the more harmful the experiment, the 'higher' the animal used, the less significant the goal, the lower the probability of success and the greater the availability of alternatives, then the less likely the experiment is to be considered ethically acceptable (see also Figure 14.1).

**Figure 14.1: Criteria for assessing the acceptability of a research project.***




When a research project falls into the opaque part of the cube, the experimental research should not be done.

* From Jennings M and Smith *J (2003) Handbook for Lay Members of Local Ethical Review Processes* (Horsham: RSPCA). Image © Patrick Bateson 1986.

14.24 In support of the acceptability of undertaking harmful research on animals rather than on humans, this view endorses the thesis set out in paragraph 3.29, according to which suffering and especially death pose greater tragedies for humans than for animals. It can follow from this argument that special consideration must be given to primates as they may suffer comparatively more than other animals from confinement and relative social isolation. For the same reason, proponents can accept a prohibition on the use of the great apes, and are inclined to apply the morally relevant criterion of 'sociability' to animals such as dogs (see paragraphs 3.44-3.46). Although the 'on balance justification' view could suggest a hierarchical order of the acceptability of using different species of animals for research, this need not necessarily be so (paragraph 3.22).[7]

14.25 Those who accept the use of animals for research purposes as defined by the A(SP)A usually also accept other uses of animals. In fact, the use of animals for food and clothing, for example, may be cited in support of research involving animals, as humans appear to be willing to sacrifice the lives and often also the quality of lives of animals, for human interests. We have already observed that such comparisons cut both ways. Thus, since the A(SP)A requires justification of harmful research, proponents of the 'on balance justification' view could be expected to explore similar justifications, albeit perhaps in a less formalised manner, with regard to other uses of animals. It is then important to relate the worthiness of the goal to the suffering of the animal involved, and the availability of alternative ways of achieving the goal. The 'on balance justification' view can therefore allow for all, or most of, the uses noted earlier on (paragraph 4.47 and Appendix 1). At the same time, it also allows for the conclusion that, although the use of animals is acceptable for many research goals, it is far less acceptable for the production of food or clothing, since in most Western societies relatively straightforward alternatives exist that could provide food and clothing without the use of animals.

[7] First, more developed animals are not necessarily more important than the less developed ones, but it is simply the case that there are more morally questionable ways of treating the more developed than the less developed. Secondly, the view can allow for the conclusion that the use of a 'less developed' animal such as a mouse is less acceptable than the use of 'higher' species, such as a primate. Pain and suffering experienced by a 'lower' species may have a much more 'global' effect than pain experienced by a higher species (see paragraph 4.17).

The value of research

14.26 Insofar as the benefits cannot be obtained by any other means, proponents of the 'on balance justification' view usually emphasise the importance of the benefits derived from pharmaceutical and toxicological research, and possibly also the value of results produced in the context of basic and applied biological and medical sciences (see also Chapters 5–9). However, some assert that a reasonable likelihood of success, in terms of a useful application of research, must be given for any experiment to be justified, particularly if it is likely to adversely affect the welfare of the research animals. Others disagree with this requirement and refer to the 'jigsaw puzzle' of science, in which almost any new research project contributes to valuable knowledge (paragraph 3.53). Nevertheless, both positions can agree that research for trivial purposes, such as the testing of new cosmetics, or of new household cleaners that differ insignificantly from already marketed products, is not justifiable.

The role of the Three Rs

14.27 The 'on balance justification' view is sympathetic towards all Three Rs provided the current level of basic and applied scientific research can be maintained, and future progress is not hindered. Possible conflicts between implementing any of the Three Rs and delaying scientific progress would usually be resolved in the interest of scientific development. With regard to Replacements, proponents note that there will always be some areas in which animal research cannot be replaced. For example, researchers studying animal behaviour such as bird flight or song will clearly not be able to undertake this research on humans. In other areas, pragmatic and ethical concerns are likely to make it impossible to replace the use of animals with humans. For example, they would argue that it would neither be practically feasible, nor ethically acceptable, to produce inbred strains of humans for genetic knock-out studies (see Chapter 7).

***The 'moral dilemma' view***

Justification for using animals in research

14.28 According to this view, most research usually poses profound ethical dilemmas, as a decision is required between two alternatives, both of which are equally morally problematic. The current scientific approach requires animals that are viewed as moral subjects to be involved in harmful research, in order to comply with the moral imperative of preventing and alleviating human suffering. However, this approach is ethically challenging to the 'moral dilemma' view, since an inclusive conception of morality regards animals as moral subjects. At the same time, if animals were not used in potentially harmful research it would be far more difficult to comply with the duty of preventing and alleviating human suffering.

14.29 An important aspect of the 'moral dilemma' view is the fact that, to some degree, the dilemma is caused by historical circumstances. For example, the present population of adults in the UK lives in an environment in which currently available products and treatments have set a benchmark for medical standards and scientific progress. Many of these products have involved animal experimentation at some stage in their research and development. The current population did not ask for the research to be undertaken, but has become used to it and benefited from its results in many ways. Accordingly, although ethical concern for the welfare of animals would demand that at least some types of research should be given up, this is difficult, because most members of society would not be prepared merely to maintain, or even to slow down, the current scientific level of research in the biomedical sciences. The moral dilemma might never have occurred if,

hypothetically, humans had never begun to experiment on animals, had had a far more restrictive policy in place or had found different ways to gain scientific knowledge.

14.30 It could be argued that the 'moral dilemma' view differs insignificantly from the 'on balance justification' view: it is simply a stronger recognition of the fact that it is morally problematic to use other species. While this may be true for some positions within the concept, it may not be for other positions. These differ with regard to the way in which the relationship between humans and animals is understood; the way in which they may be used; views about the value of research; and the role of alternatives.

14.31 Proponents of the 'moral dilemma' view are less certain than those holding the 'on balance justification' view about the supremacy of humans over animals. There can be various reasons for this difference. Usually, interpretations of religious approaches or evolutionary theory which suggest a clear primacy of humans over animals are rejected as they could equally be used to argue for stewardship and compassion (see also paragraphs 3.21, 3.24 and 3.27–3.50). Rather, proponents may draw on religious arguments that recognise human stewardship over animals,[8] or they assert that it is reasonable to assume that animals become members of the moral community insofar as they possess one or more of the morally relevant capacities discussed in Chapter 3 (paragraphs 3.27–3.50). Whereas within the 'on balance justification' view there is usually acceptance of a hierarchy of species based on the aggregate number of morally relevant capacities within the 'moral dilemma' view a more commonly found position is that there is no such hierarchy.

14.32 Similarly, whereas those holding the 'on balance justification' view perceive forced consequentialist sacrifice as practised under the A(SP)A as acceptable because they take the view that it matters less to the animals themselves whether or not they are used in research, some proponents of the 'moral dilemma' view disagree. The reason for scepticism can be called *epistemic modesty*: most proponents of the 'on balance justification' view assert that it is usually possible to assess levels of pain, suffering and distress in scientifically reliable ways. Some of those holding the 'moral dilemma' view are more cautious. They refer to philosophical problems resulting from the 'problem of other minds', which casts doubt over the possibility of determining the exact state of consciousness of other beings (paragraphs 4.5 and 4.22). Since skilful observation, free from inappropriate anthropomorphisms, strongly suggests that animals do possess a range of different welfare states, one should, where possible, err on the safe side and refrain from any harmful use. Similarly, one should not assume that just because an animal such as a mouse is not in possession of higher mental capacities it is therefore more acceptable to subject it to pain: as may also be acknowledged under the 'on balance justification' view, the quality of the pain and suffering may have a far greater intensity, despite, or rather because of, the lack of higher capacities (paragraphs 3.29 and 4.17).

14.33 In conclusion, from the 'moral dilemma' view, the primary motivation for granting animals intrinsic moral status is their possession of any of the morally relevant features. Expanding the discussion of the morally relevant criterion of sociability, proponents emphasise the importance of what can be termed *relationship morality*: humans can build meaningful relationships not only with other humans, but also with animals. The way specific areas of well-being are influenced by human action matters equally in both cases, since both are subjects of life (see Box 3.4) who have interests in maximising their welfare. Disrespecting the *prima facie* entitlement of animals to lead a life free from negative interference by humans can therefore create an existential dilemma for proponents of this position.

8 However, see footnote 3.

14.34 The question remains as to why humans should be able to use animals for harmful research. Proponents of the 'moral dilemma' view simply acknowledge that an uncontroversial justification cannot be obtained. Others may refer to the solidaristic preference argument (see paragraph 14.13), observing that while humans have difficulties in assessing the exact welfare-related states of animals, they have far fewer difficulties in assessing mental states relating to pain, suffering and distress in other humans. This capacity for empathy, together with the familiarity of suffering from one's own experience, leads to strong desires to help alleviate, and where possible prevent, suffering in fellow humans, even if this is at the expense of disregard for the interests of some animals.

Using animals in research and in other contexts

14.35 It is difficult to predict what kind of research would be acceptable according to this view. The following aims to provide an outline of types of research that proponents of the view could accept. In many cases the 'moral dilemma' view might be more restrictive than the 'on balance justification' view in permitting harmful research (provided the goals are comparable). But in some areas it also appears to allow for an extension. Whereas according to the 'on balance justification' view research on the great apes, such as chimpanzees, is usually prohibited, within the 'moral dilemma' view this need not be the case. For example, the role of chimpanzees in the development of a test to identify hepatitis C-contaminated blood and blood products had a major impact on decreasing human morbidity and mortality (paragraph 6.25). Such research would not currently be permissible in the UK. However, under the 'moral dilemma' view it could, in principle, be acceptable, albeit with grave regret.

14.36 With regard to other uses of animals, holders of the 'moral dilemma' view are most often reluctant to accept them: insofar as other practices involve avoidable degrees of pain, suffering and distress, which are not to the benefit of the animal involved, the use is not ethically acceptable. Since proponents of the approach can also be understood to be sceptical as to how far humans will ever be able to understand what it is like to be another species, they would usually seek to avoid the use of animals for purposes such as the production of food and clothing, and sport and entertainment, particularly since in most Western societies alternatives to the same goals are readily available.

The value of research

14.37 The moral dilemma results from the fact that a valuable good such as the development of a medicine for a severe disease for one type of moral subject (i.e. humans) conflicts with a valuable good of another moral subject (i.e. that of an animal), usually its welfare or life. This means that no conflicts need exist when the human good is comparatively trivial. Cases of trivial goods that should not be developed would include new household cleaners that are similar in all relevant qualities to a number of other already available products, or analogous cases. Similarly, the approach would require that robust mechanisms be put in place to avoid the duplication of research, be it in the academic or commercial context. This is especially important with regard to the production of GM animals and cloning, as these procedures use relatively large numbers of animals, and, in some cases, may have unpredictable implications for welfare (paragraph 4.57).

14.38 Since proponents of the 'moral dilemma' view are very concerned about possible welfare infringements and accept them only in cases where a substantial benefit is to be expected, the question of basic research poses difficulties for the approach. On the 'on balance justification' view, a wide range of basic research can be permissible. But on the 'moral dilemma' view the likelihood for any useful application to arise from knowledge gained in

basic research will need to be considered carefully. Many proponents argue that if results from basic research are unlikely to ever contribute to any practical application, the research would not be permissible, unless the welfare infringements are very minimal.

The role of the Three Rs

14.39 Due to the existential nature of the conflict, the moral dilemma is a situation that moral agents will seek to avoid as far as possible. Since they wish to protect the goods of both animals and humans, there is a great urgency to implement the Three Rs, with particular emphasis on Replacements. Just as proponents of the approach urge those wishing to undertake research on animals to justify its necessity clearly, they urge that every effort be made to ensure that the potential of alternatives is exhausted as far as possible.

14.40 They therefore welcome the provision of the A(SP)A, according to which animals can only be used for research if there is no other way of obtaining the information. However, they also argue that in order for this requirement to carry ethical weight (in the sense that the use of animals is therefore more acceptable), genuine efforts must be made to develop replacements, and to overcome the obstacles to their development and implementation (paragraph 3.63 and Chapter 11). Similarly, there is a strong obligation on those using animals in the commercial sector. For example, the view can be taken that not all products developed by the pharmaceutical industry justify the resolution of the moral conflict between the interests of animals and humans in favour of the latter. Companies operate in competitive environments, in which the primary aim is to generate profits, by focusing on those interventions that generate the highest returns. These products are not always those that are most needed (paragraphs 3.13, 8.7 and 15.83). Whereas, from the 'on balance justification' viewpoint, there was no reason to object to this *modus operandi* in principle, here it can be argued that such interventions are only justified if they do not involve harmful research on animals.

***The 'abolitionist' view***

Justification for using animals in research

14.41 According to this view, there is no justification for any harmful research on sentient animals that is not to the benefit of the animal concerned. This is valid irrespective of any possible scientific, medical or other benefit. Since humans should not act in morally objectionable ways, proponents argue that every effort must be made to bring an end to all research involving as soon as possible. Research on animals is viewed as unacceptable because any research constitutes forced consequentialist sacrifice which can come in two forms (see paragraph 15.5):

- First, animals can be used to produce results that benefit other animals. For example, research may seek to develop a vaccine for cattle. The animals directly involved in research are used without consent, which is impossible to obtain from animals. The research animals are hence forced to experience a range of negative welfare infringements for the benefit of other animals.
- Secondly, animals can be used in research undertaken for the benefit of humans. The examples provided in Chapters 5–9 show that the welfare implications of harmful research are diverse and include research such as toxicity testing and the use of animals as disease models, both of which may cause considerable suffering. The breeding, transportation and housing conditions will also affect the animal (see paragraphs 4.31–4.59).

14.42 From the abolitionist viewpoint, the justification that proponents of research involving animals provide, for logical reasons, cannot support their case. The fundamental question

that abolitionists pose is why the moral capacity of an animal should count less than that of a human. The question to be answered is therefore: why should the suffering of a mouse be morally less significant than the suffering of a human? The answer usually provided is that the human is more important. Most abolitionists are willing to concede that such differences in status can justify unequal treatment in the case of competition for goods; for example, it could be argued that it is morally unproblematic for humans to prevent animals from eating the fruit of a tree by covering it with a net. However, abolitionists also argue that such difference in status cannot in itself justify the use of animals by humans for harmful research.

14.43 Similarly, abolitionists disagree with the argument that suffering experienced by animals is experienced in a lesser way than the suffering of humans. Quite plausibly, the nature of suffering differs between different species, but as is obvious from the discussion in Chapter 4, biological similarities, the responsible use of empathy[9] and critical anthropomorphism emphasise the reality of animal suffering (paragraph 4.60). While, strictly speaking, it may be true that we will never really know 'what is like to be a rat' (see paragraph 4.5), in the absence of evidence about the different natures of suffering, humans should err on the side of caution and not make the assumption that animals suffer in a lesser way.[10]

14.44 According to the 'abolitionist' view, the main reasons why humans find it acceptable to use animals stem from societal conventions. Humans continue to use animals because they have always done so. In moral terms this conclusion can be called a *genetic fallacy*: the moral permissibility of actions does not follow simply from previously established practices. Rather, all actions need to be justified by reference to ethical theories. Since, on the 'abolitionist' view, all animals and humans capable of sentience have the same moral status, use of animals for research constitutes unjustified discrimination and illegitimate use of force by one member of the moral community against another. Such use of force that ultimately may bring about death is only justified in cases of emergencies, such as self-defence. This circumstance does not apply in the case of commonly conducted harmful animal research. Thus, from the 'abolitionist' view, the current treatment of most animals in Western societies is adequately described as speciesist (see Box 3.4 and paragraph 4.13): the primary criterion that distinguishes animals from humans is their belonging to different species. However, on the 'abolitionist' view, this is a morally irrelevant criterion. It cannot justify differential treatment of humans and animals any more than different sex or race of humans can justify differential moral treatment.

Using animals in research and in other contexts

14.45 As in the 'moral dilemma' view, the 'abolitionist' view concludes that the consideration of the use of animals in research must lead to a re-evaluation of uses of animals in other contexts. Insofar as other practices involve avoidable degrees of pain, suffering and distress, which arise from a practice that is not to the benefit of the animal involved, other uses are not ethically acceptable. Consequently, they seek to avoid the harmful use of animals for purposes such as the production of food and clothing, or for sport and entertainment. More difficult cases may be raised by the issue of pest control. Most abolitionists would employ barrier methods of control that cause minimum stress and suffering to the animals concerned. Alternatively, they can decide to abstain from any control. Others may argue

9 Thomas D (2005) Laboratory animals and the art of empathy *J Med Ethics* **31**: 197–202.

10 It is also possible to assume that the suffering of animals is actually experienced in a much more severe way than that of humans. For example where they do not have the possibility of 'understanding why they suffer', which can provide considerably relief in the case of humans.

that temporary suffering, resulting for example from catching the animal and moving it to another environment, can be justified, provided that the new environment is comparable in quality to the previous one.

The value of research

14.46 The main concern of the 'abolitionist' view is the capacity of beings to suffer. Therefore, and in agreement with the previous three positions, research to alleviate suffering of humans and animals is imperative. But this imperative is constrained by the fact that research itself must not cause any suffering to beings unable to consent to such treatment. Therefore, proponents see research on voluntarily consenting humans, or Replacements such as *in vitro* research or computer studies (see Box 11.1), as the only ethically acceptable solutions. Abolitionists also frequently argue that a focus on research with human participants improves scientific practice, as it circumvents problems concerning predictability and transferability of scientific results from animals to humans (paragraph 10.27).

14.47 A possible problem for this approach is how to deal with the consequences of a scenario where all animal research was in fact abandoned. Would it be possible to maintain an equivalent level of basic and applied scientific knowledge without the use of animals in research? One response is to point to the potential of human creativity: throughout human history, an impressive range of inventions has been achieved, which have allowed humans to attain goals that were thought as categorically impossible in earlier periods. For example, few people would have believed a person in the mid-19th century who stated that it would one day be possible to fly to the moon. Put differently, the argument might also be presented in the form of a thought experiment: if a powerful alien race invaded Earth and demanded an end to all animal research, as otherwise all humans would be killed, would it not be likely that human creativity would very quickly develop a range of alternative methods to take the place of the previously practised animal experiments?

14.48 This paraphrase of the argument that 'necessity is the mother of invention' is also used to draw attention to the fact that achieving changes in policy is not always only a question of small incremental changes, but more often a matter of powerful incentives. Thus, proponents emphasise that radical changes are possible, as long as there is a political will at national and international levels to achieve a change. Recent developments such as bans on the use of animals for the testing of cosmetic products and their ingredients, alcohol or tobacco, and the policy decision not to grant licences for the use of the great apes in the UK, are also cited to support the argument that substantial change is possible.

14.49 All proponents need to consider another issue arising from the scenario of a sudden abandonment of animal research. It can plausibly be argued that the pace of most areas of research would slow down, and that the development of new medicines would be delayed, provided that, in principle, Replacements and studies on humans could fill the gap of animal research in the medium to long term. Many abolitionists respond by making reference to the 'historical contingency' argument which featured in the 'moral dilemma' view (paragraph 14.29). Abolitionists note that present day generations simply 'inherited' animal research and its consequences without consent. They argue that irrespective of the costs for humans, the immediate cessation of animal research is ethically superior to a compromise solution, in which a 'phase-out' approach is sought, for example by introducing further restrictive policies. But some advocate instead the need of more direct action, for example in the form of freeing animals from research facilities. Others acknowledge pragmatic political and professional constraints, and conclude that the scenario of a sudden end to all animal research is highly unrealistic. Even if there was a political will to ban all such research, in view of the practical realities, the transition would

inevitably be 'soft'. Accordingly, from the 'abolitionist' view the proactive development of Replacements is crucial in achieving a smooth and quick transition.

14.50 We observed above that the development of these alternatives faces considerable scientific and non-scientific challenges (paragraphs 11.6–11.9 and 11.19). There is also one type of research that cannot be replaced. This concerns harmful studies to understand the basic biological processes, behaviour and evolution of animals for the sake of advancing knowledge. The problem here would be that this research cannot be undertaken on humans, since the goal is not to learn about the human, but about the animal organism. However, appropriately conducted non-harmful and purely observational research on animals in their natural environment could be permissible. While those taking the 'abolitionist' view are, in principle, concerned about any harmful use of animals that is not in their interest, many are particularly concerned about research in which animals are sacrificed for comparatively trivial benefits to humans, agreeing with the position discussed under the 'moral dilemma' view (paragraph 14.36).

The role of the Three Rs

14.51 Since on the 'abolitionist' view any forced consequentialist sacrifice is ethically unacceptable, strictly speaking the options of Refinement and Reduction strategies are not compatible with the approach.[11] The focus is therefore usually on Replacements only, which need to be developed, validated and implemented as a matter of urgency.

The 'weakness of morality' view

14.52 At this point, we can briefly consider one last view, which can be seen as a sub-category of the 'abolitionist' view and can be called the 'weakness of morality' view. Proponents agree with the abolitionists that from a moral point of view it is simply wrong to use animals for any human purposes that compromise the welfare of animals in ways that are not in their interest. Despite this belief, they find that they are not motivated to act on it, just as many people think that, morally, they should give more money to charity, or cease eating meat, or act in a more environmentally friendly way, but never actually do so. In the case of research involving animals, such people believe that the benefits to humans, although improperly gained, overwhelm their moral qualms, which exist at the level of conscience only. Thus, they do not act on their belief that research involving animals is wrong, by boycotting products tested on animals or attempting to bring about social change by changing moral attitudes. Unlike the true abolitionists, they may even believe that, in general, moral advocacy is too weak a motivating force at the level of each individual human. However, they have greater hopes for structural change. From this viewpoint, implementation of all Three Rs, and particularly replacement strategies, holds out the hope that it may be possible to achieve scientific goals without being complicit in immoral behaviour, by making research involving animals unnecessary.

## Public policy in the context of moral disagreement

14.53 It is clear, then, that great moral disagreement exists both within and outside the Working Party. Nevertheless, as in other areas of ethically contentious issues, such as abortion or euthanasia, any society needs to settle on a single policy for practical purposes. Thus steps

11 Since the approach is primarily concerned with the avoidance of suffering *de facto*, the application of Refinement and Reduction could be viewed as steps towards the ultimate goals of replacement, especially insofar as they help to alleviate animal suffering. But this view is not shared by all of those taking the abolitionist position.

need to be taken to reduce existing disagreement as far as possible. At the very least, if a public policy is adopted which many believe to be morally wrong, instability, protest and, in extreme cases civil unrest may ensue. In thinking through the next stage in the argument we are partially influenced by the concept of the 'overlapping consensus', developed by the American philosopher John Rawls, who considered how to achieve fair agreements between reasonable moral agents on policies and procedures in societies that faced the 'fact of pluralism'.[12] The concept relies on the possibility that each party to a consensus supports it for its own sake, or on its own merits, based on its individual moral or other normative framework.[13]

14.54 In trying to achieve an overlapping consensus it is necessary to produce a procedure or position that could be adopted from all reasonable perspectives. Could it be the case that the concept of the Three Rs, and the type of hybrid moral position (some absolute constraints, some balancing), which can be said to underlie the A(SP)A, could be accepted, at least in broad outlines, by all positions? This is clearly so for the cluster of moral positions that support the 'on balance justification' view, which directly endorses such a regime. The 'moral dilemma' approach suggests that there are no decisive moral considerations, and so may, for practical purposes, be prepared to fall in line with the 'on balance justification' view, as long as the research is genuinely necessary, and no alternatives exist. The 'weakness of morality' view as a sub-category of the 'abolitionist' view cannot accept that there is a moral justification for present practices, but at the same time does not see morality as having influence on behaviour in any relevant sense. Its proponents, too, can accept something akin to the current regulations as a practical solution. Hence between these three views a form of overlapping consensus can be achieved.

14.55 However, whereas the 'anything goes' view can accept the permissions included in the current regulations, it cannot accept the restrictions. The position for the abolitionists is the converse: they can accept the restrictions but not the permissions. As these moral positions appear to fall outside this overlapping consensus they require special discussion.

14.56 Although it is, as we have said, unlikely that any serious thinker holds the view that human beings may do whatever they like to animals without any moral justification, nevertheless there are groups who view some current restrictions as unjustified. Could anything be done to bring such groups into the overlapping consensus? The place in which their disagreement is greatest concerns cases such as the policy of the *de facto* ban on using the great apes. Proponents of the 'anything goes' view argue that when there is a very good chance of providing positive results, of potential value to human health and life, then some forms of research on great apes should be permitted. The circumstances in which this would be permissible, and the forms of permissible treatment of such animals, would be very tightly controlled, to a point where, in practice, it may be very rare indeed that the conditions are met. As observed above, the current 'ban' merely has the status of policy, and is not enshrined directly in the A(SP)A (paragraphs 13.6 and 13.30). Thus, in principle, some of the proponents of the 'anything goes' view might join the overlapping consensus, as long as the prohibition is not a matter of law.

14.57 The abolitionists, by contrast, would prefer the policy decision to be a matter of law, rather than policy. They welcome the restrictions in current regulations, yet view the permissions as unacceptable. Widening the permissions would make matters worse for them. The

12 Rawls J (1987) The Idea of an Overlapping Consensus *Oxford Journal for Legal Studies* **7**: 1-25.

13 Rawls J (1989) The Domain of the Political and Overlapping Consensus *New York University Law Review* **64**: 233–55.

argument for this is, as we have seen, either that it is wrong to take the life of an animal or that it is wrong to impose suffering on one being for the sake of another. This argument is also accepted by those who hold the 'weakness of morality' position and the 'moral dilemma' argument, and hence is accepted by a broader group than the abolitionists. There is therefore also a consensus between these three groups on the immorality of research involving animals. Only the abolitionists believe that it provides a decisive reason for ending harmful research upon animals.

14.58 Yet, it would be imprudent to abandon the project of trying to draw more people sharing the abolitionists' view into the overlapping consensus. This would, of course, mean introducing more restrictions. Some restrictions might easily suggest themselves; for example, those where animals are being used to develop consumer products with relatively trivial consumer or health benefit, to produce products which differ little from those already on the market, where research is being duplicated or where alternative methods could be developed if there was a political will to do so. Hence by being clearer about the circumstances in which research involving animals is permitted, there is some chance of creating an overlapping consensus which would gain broader, albeit not universal, approval.

14.59 In sum, the way to try to draw more people into the broad consensus is to examine cases where restrictions may seem to rule out very significant research, and cases where permissions allow relatively trivial work. By fine-tuning the regulations, relaxing some restrictions and introducing others, a broader group of people could give a greater endorsement to the regulations than has been possible before now, even if no one set of regulations would be considered fully acceptable by all.

14.60 In aiming to include the 'abolitionist' and the 'anything goes' views in the overlapping consensus it has also become clear that their willingness to adhere to the consensus differs somewhat from the 'on balance justification', the 'moral dilemma' and the 'weakness of morality' views. Whereas the latter three views are able to genuinely *share a consensus*, the former two appear at best to be able to accept the approach of the Three Rs and the provisions and practise of the A(SP)A under given current circumstances as a *compromise*. Thus, it would seem wrong to suggest that there can be *substantive consensus* (i.e. consensus on a shared view about which research can be viewed as justified), although it seems correct to say that in view of the current situation an enlarged *procedural consensus* is achievable (i.e. consensus that a certain system of licensing and control of animal research is tolerable or acceptable).

14.61 This distinction is important for two reasons. First, because policy should not be guided by what in effect may simply be the lowest common denominator. Rather, as we have said, we recognise that there are a number of competing moral outlooks on animal research, which need to be considered in shaping policy that is defensible and reasonable, and with which as many members of the public as possible can agree. Too often, the polarised character of the debate has obscured potential areas of genuine agreement, and it is crucial to examine, as far as possible, its potential scope.

14.62 Secondly, although full substantive consensus may be unattainable, we conclude that there is genuine overlapping consensus in terms of process. Even if proponents of the 'anything goes' view and the 'abolitionist' view differ on the letter of the law of the A(SP)A, current government policy and how these are implemented, most reasonable proponents of both views are likely to accept that for as long as animal research continues, animals involved must be protected. It can be argued that in these circumstances a detailed system of licensing and inspection is a necessary and legitimate instrument to reconcile the different views that stakeholders and members of society hold.

14.63 If this approach is to count as a fair process, several conditions need to be met. First, all involved need to be able to have access to relevant information about animal research, such as the goals, welfare implications and alternatives to research, in order to judge whether specific types of research and mechanisms to regulate them are justifiable with regard to their normative frameworks. Secondly, the discussion about appropriate policies must be conducted in a fair and informed manner, which permits all reasonable participants to argue their case. In this context, specific forms of protest that involve militant protests and violence are highly damaging and erode the necessary climate for reasoned debate. Thirdly, there must be a genuine possibility for policies to be readjusted if the consensus shifts. Fourthly, in order to do so there must be reliable evidence on the views of all stakeholders as to whether they can support the *status quo*, and any future developments. Thus, only if these conditions are met can it be argued that the A(SP)A, which represents a hybrid framework combining deontological and consequentialist elements (see paragraphs 3.58–3.62), is justified as, in practice, it could be endorsed by the vast majority of members of the pluralist UK society.[14] We present further discussion on more detailed aspects of improving policy and the climate of debate about animal research in the next chapter.

14 Similar approaches can be found in other areas of bioethics-related policy: for example, although people in the UK have a *prima facie* right to confidentiality, this right can be infringed in cases where it is in the public interest, since it is accepted practice that medical records can be accessed without prior consent in the case of criminal investigations.

# Chapter 15

## Discussion and recommendations

# Discussion and recommendations

## Introduction

15.1 More can and must be done to improve the quality of the debate about research involving animals. Some of those who oppose such research accuse those in favour of acting without any legitimate ethical motives, and vice versa. We hope that the discussion in Chapter 14 has helped to show that such generalisations are mistaken, and that a highly complex picture emerges when the various positions are taken seriously.

15.2 We observed that the positions are not categorically distinct, but should rather be viewed as positions on a spectrum. Within this spectrum there is a significant area of common ground, shared by all members of the Working Party, despite their differences with regard to other issues. We describe this area of agreement below in the form of a *consensus statement*. Several practical implications that follow are explained in more detail in the conclusions and recommendations which are based on the recognition that all animal research needs to be justified. We address:

- ways of improving the quality of debate about research involving animals in society (paragraphs 15.22–15.52);
- the role of legislation and regulation (paragraphs 15.53–15.56);
- the development and implementation of the Three Rs (paragraphs 15.57–15.62); and
- a range of more specific issues, which include:
  - ways of motivating and monitoring approaches to reduction of the use of animals in research (paragraphs 15.64–15.67),
  - issues raised by the possibility that research is duplicated (paragraphs 15.65–15.70),
  - the use of GM animals (paragraphs 15.71–15.75),
  - the scientific validity of animal experimentation (paragraphs 15.76–15.80),
  - toxicity testing (paragraphs 15.81–15.83),
  - problems in harmonising international test guidelines (paragraphs 15.84–15.87), and
  - UK researchers commissioning or undertaking research abroad (paragraphs 15.88-15.91).

## Consensus statement by all members of the Working Party

***Research involving animals and other uses of animals***

15.3 It is important to consider the ethical issues raised by animal experimentation in the wider context of the other uses of animals in society, and to take into account:

- the impact on the lives and welfare of animals that different uses have;
- the broader consequences if there were a ban on using animals in specific circumstances;
- a comparison of the benefits arising from the different uses of animals; and
- the numbers of animals involved.

15.4 The involvement of animals in research cannot be justified simply by the fact that animals are used or abused in other ways. Each use requires special consideration. Members of the Working Party noted during their own discussions, and in considering responses to the Consultation, that views on animal research were not always consistent with views on the

other uses of animals. Awareness that contradictory views are often held simultaneously is an important first step in considering the ethical issues raised by research involving animals.

***The benefits of research involving animals***

15.5 Historically, animals have been used in a wide range of scientific research activities that have provided many benefits to society, particularly in relation to the advancement of scientific knowledge, human and veterinary medicine and the safety of chemical products.

15.6 Some of these advances might have been achieved by other means, although we cannot know this. Neither can we know what a world would look like in which animal research had never been undertaken. Hypothetically, there may have been other options that could have produced acceptable levels of knowledge and healthcare. These levels might have been lower than our current standards, but perhaps if society had deemed the use of animals for research as unacceptable there would have been acceptance of greater limitations on scientific and medical progress. Alternatively, it is conceivable that equally good or better progress might have been achieved with other methods. The Working Party agreed that speculation about whether or not acceptable standards in basic and applied research could have been achieved in the past by means other than the use of animals is less important than the question of assessing the consequences of continuing or abandoning animal experimentation now.

15.7 It is sometimes assumed that to end animal research would be to end scientific and medical progress, but such generalisation is unhelpful. The UK Government has responded to changes in the moral climate by introducing policies that have ended some types of animal research and testing in the UK. For example the use of animals for the testing of cosmetic products and their ingredients, alcohol and tobacco has ceased. Similar policies are in place regarding the use of the great apes. Independent of the moral acceptability of research, the scientific costs and benefits of abandoning specific types of animal research need to be assessed on a case by case basis. On the one hand, the possibility of the emergence of new diseases may require a reassessment of whether the abandonment of specific types of research is still justified. On the other, scientific advances that could replace the use of animals in some areas may enjoin us to assess whether further policies should be introduced to terminate these uses of animals accordingly.

15.8 The validity, usefulness and relevance of specific types of animal research, for example in relation to the use of animals for the study of human diseases, needs to be ascertained in each individual case.

***Desirability of a world without animal research***

15.9 All research licensed in the UK under the A(SP)A has the potential to cause pain, suffering, distress or lasting harm to the animals used. Most animals are killed at the end of experiments. A world in which the important benefits of such research could be achieved without causing pain, suffering, distress, lasting harm or death to animals involved in research must be the ultimate goal.

15.10 We have considered the different arguments advanced in favour of and against continuing specific types of animal research in Chapters 3 and 14. Some believe the imperative to protect animal welfare should be overriding, whereas others believe that the moral arguments favour the continuation of research on animals. All members of the Working Party acknowledged that these viewpoints arise from moral convictions that should be given serious consideration. This approach requires open-mindedness in trying to understand the reasons and arguments of others. Genuine willingness is also required to test and, where necessary, revise one's own moral framework.

15.11 While we trust that more progress in the moral debate can be made, we are aware that, for the near future, further moral argument alone cannot provide a universal answer as to whether or not research on animals is justified. But practical advances in scientific methods can reduce areas of conflict. For this reason, the importance of the Three Rs, and especially of the need to find Replacements, cannot be overstated.

***The ethical importance of the Three Rs***

15.12 The Working Party therefore concludes that it is crucial that the Three Rs are, and continue to be, enshrined in UK regulation on research involving animals. The principle that animals may only be used for research if there is no other way of obtaining the results anticipated from an experiment is also fundamental.[1] Furthermore, we observe that for moral justification of animal research it is insufficient to consider only those alternatives that are practicably available at the time of assessing a licence application. The question of why alternatives are not available, and what is required to make them available, must also be asked. The potential of the Three Rs is far from being exhausted. The Working Party therefore agrees that there is a moral imperative to develop as a priority scientifically rigorous and validated alternative methods for those areas in which Replacements do not currently exist. It is equally important to devise mechanisms that help in the practical implementation of available validated methods.

15.13 In applying the Three Rs it is crucial to consider not only the context of the experiments but also the many other factors that can affect animal welfare, including breeding, transportation, feeding, housing, and handling. The quality of these factors, and the ability of animals to satisfy their species-specific needs, can usually be improved.

***Regulation***

15.14 We acknowledge that the UK has the most detailed legislative framework regarding animal research in the world. But proper attention to the welfare of animals involved in research and the accountability of scientists who conduct animal research cannot be achieved merely by having detailed regulations. Regulation can act as an emotional screen between the researcher and an animal, possibly encouraging researchers to believe that simply to conform to regulations is to act in a moral way. It is therefore crucial to promote best practice more actively and to improve the culture of care in establishments licensed to conduct experiments on animals.

15.15 When considering the replacement of specific types of research by alternative methods, it is important to take account of the international context in which research involving animals takes place. Many chemical and pharmaceutical compounds that have been developed are being marketed in countries or regions that have different regulatory frameworks for animal research and testing. Alternatives have been internationally accepted for safety testing. Nonetheless, many Replacements are not universally accepted, and the process of validation is lengthy. These processes need to be optimised and initiatives aimed at abandoning and replacing specific types of animal testing at national levels complemented by initiatives at the international level. This is not to say that initiatives in the UK can only be taken once there is consensus at an international level. In the past, the UK has been a leader in working towards change in international policies related to research involving animals. This leadership should be encouraged.

1 A(SP)A, Section 5 (a).

***Duplication of experiments on animals***

15.16 Scientific experiments involving animals are sometimes repeated by the same or other research groups. In considering whether the repetition of experiments should take place, it is important to distinguish between *duplication* and *replication* of experiments:[2]

- Duplication of harmful animal experiments is in principle unacceptable. We use the term to describe cases where there is insufficient scientific justification for the repetition. It occurs primarily when the scientist either does not know that another has carried out the experiment or test in question, or when he does know but is unable to attain reasonable access to the information.
- Replication refers to repetition of experiments or tests when this is necessary for sound progress in scientific enquiries. The scientific method demands that research findings need to be corroborated by the same and other research groups in order to establish the validity of the results.

15.17 The Working Party acknowledges that academic competitiveness and commercial confidentiality can sometimes complicate the sharing of information. But at its best, science is an open process, and mechanisms that prevent the sharing of information need to be reviewed carefully in terms of their justification and implications for the use of animals in research.

***The context of the debate***

15.18 The majority of researchers who use animals consider that, despite progress in the implementation of the Three Rs, animal research will remain an essential part of their work. Furthermore, the current regulatory frameworks for approval of chemical products and medicines require tests involving animals. We conclude that it is unrealistic to assume that all experiments on animals will end in the short term. It is crucial, therefore, to create a climate in which the necessity and justification for using animals is assessed and discussed fairly, and with due respect for all views.

15.19 Constructive debate would be facilitated by the provision of clear information about the full implications of research involving animals in terms of the numbers and species of animals used, as well as the pain, suffering and distress to which they are subjected. It is also important that society should be informed about the scientific, medical and other benefits of animal research. Information about selected aspects of research without provision of any further context can be misleading.

15.20 All members of the Working Party agreed that the use of violence and intimidation against members of the research community, research institutions, their business partners, family and neighbours, or against organisations and individuals representing animal welfare groups, is morally wrong and politically insidious. The freedom to promote or oppose research involving animals peacefully and democratically, however, must be maintained.

## Conclusions and recommendations

15.21 Before we present the conclusions and recommendations, we must clarify two important points:

- Members of the Working Party who believe that research using animals is, on balance, justified, as well as those members who take the view that it poses a moral dilemma,

2 Animals are sometimes used in repeated experiments for the purpose of education or training. We have not addressed the issues raised by this particular use, see paragraph 1.18.

find most research which is currently undertaken to be acceptable. They are cautious of any proposals that might undermine progress in basic and applied sciences which, they believe, in specific areas crucially depends on research involving animals. Other members who, within the spectrum of possible views, are closer to the abolitionist view, are implacably opposed to the use of sentient animals for any scientific or medical purposes, and assert that other methods must be used to ensure progress. They are equally cautious of any proposals that prolong or legitimise the infliction of pain and suffering on sentient animals. We emphasise that the recommendations that follow below, several of which aim to improve the conditions in which animals are used, should not be taken to imply the acquiescence of the latter group to animal experimentation. These members acknowledge that animals are currently subjected to experiments and believe that they need protection. While they continue to advocate that the recommendations should go further in specific areas, they accept them as steps in the right direction, without endorsing research involving animals in principle.

- Because of the diversity of views and beliefs within the Working Party, it has not been possible to achieve complete agreement on all of the recommendations by all members of the group. In our discussions, however, and in discussion with the Council, it became clear that in the context of a highly polarised debate it is crucial to make unambiguous recommendations in specific areas. While it is therefore not possible to attribute to all members of the group the conclusions and recommendations presented on any one issue, all members do accept the recommendations as valid contributions to the debate, clarifying further important implications of the more abstract thoughts presented in the consensus statement above. Nonetheless, on a few occasions it did not prove possible to identify positions that were acceptable to all members. In such instances we have tried to explain the reasons why some members could not agree with particular conclusions or recommendations. We hope that the descriptions of disagreement help to clarify the nature of the underlying dispute in a constructive way.

### *The context of the debate*

*General observations*

15.22 Members of the research community who use animals in their work frequently refer to evidence from opinion polls to support their claim that most people support research on animals because of the benefits to humans. They take the view that more information on the benefits of research involving animals would help engender further support from the public. Those who are fundamentally opposed to research involving animals, and those who are primarily concerned about the pain and suffering it may cause, also use evidence from opinion polls to support their views. They often claim that most people would share their views if only they knew more about the welfare implications of research. While evidence from opinion polls should be treated with some caution (paragraph 1.16), many people would like more information on research involving animals, some asserting that it takes place in secret (see paragraph 2.19).

15.23 One response to this situation would be to improve transparency and openness, which should serve the interests of all the various parties concerned with issues raised by animal research. Freedom of information is crucial to informed debate in democratic pluralistic societies (paragraph 14.63). Increased openness and transparency should therefore be encouraged, subject to safeguards for confidentiality of proprietary information and assurances that the safety and security of those involved in animal experimentation will not be compromised. Such an approach would also be consistent with the requirements of the FoI Act (Box 13.4).

15.24 We therefore consider first how provision of information by the Home Office can be improved, especially in relation to the presentation of the *Statistics*, details about granted licences for research and the way the cost-benefit assessment is carried out. We then explore ways in which discussion between those involved in research and interested stakeholders can be improved; consider issues raised by the conduct of public debates on animal experimentation; and review the role of scientists, campaigning organisations and teachers in education and higher education. We also comment on the practice of using violence and intimidation as means of protest against animal research.

*Provision of information by the Home Office*

Statistical information about the number of animals used and the suffering involved

15.25 The *Annual Statistics of Scientific Procedures on Animals,* published by the Home Office, have an important role in providing information about animal experimentation. At the same time, there is wide agreement that the data are presented in ways that are not readily accessible to lay people, and that the presentation could be improved. In particular, the *Statistics* have been criticised for not providing clear answers to the following questions: (i) what is the nature, level and duration of pain, suffering and distress actually experienced by animals used in the different kinds of procedures? and (ii) how many animals are used in procedures and related activities?

15.26 It is not possible to answer the first question, because information about welfare implications is only provided prospectively, in the process of the licence application (see paragraph 13.14). By definition, it is not possible to know in advance how animals will be affected in practice, and data from separate interim or retrospective analyses are not reported publicly.

15.27 Information about the degree of pain and suffering can, in some sense, be inferred from the *Statistics* about the severity bands assigned to granted project licences. These are classified in one of three bands: *mild, moderate* or *substantial* (see Box 13.3). But over the five-year period of a project licence, a range of different protocols, themselves assigned different severity limits, may be carried out. It is questionable how meaningful it is to average out the different limits under one band, in order to provide the public with accurate information. For example, it may be the case that a project that contains ten mild protocols, each involving 10,000 animals, and one protocol with a substantial severity limit involving 50 animals, would still be classified as mild.[3] Furthermore, it has also been suggested that the category of moderate protocols 'appears to be something of a catchall, covering a wide range of the more invasive procedures'.[4] We make the following observations.

15.28 Information about the suffering that animals involved in procedures experience in practice is unsatisfactory. **We recommend that the Home Office should make retrospective information about the level of suffering involved during procedures publicly available. In gathering this information the Home Office should also obtain and make available, retrospectively, information about the extent to which the scientific objectives set out in applications have been achieved.**

3 Animals Procedures Committee (2003) *Review of cost-benefit assessment in the use of animals in research*, p44, available at: http://www.apc.gov.uk/reference/costbenefit.pdf. Accessed on: 4 April 2005.

4 Animals Procedures Committee (2003) *Review of cost-benefit assessment in the use of animals in research*, p44, available at: http://www.apc.gov.uk/reference/costbenefit.pdf. Accessed on: 4 April 2005.

15.29 The terminology used to describe the severity of projects and individual protocols and procedures is not straightforward and therefore difficult for members of the public to understand. **We recommend that the annual *Statistics* should provide case studies of projects and procedures that were categorised as *unclassified, mild, moderate* or *substantial*. Case studies should also include examples of animals used over extended periods of time and should describe not only their immediate involvement in research but also the range of factors that influenced their life experiences, such as the conditions of breeding, housing and handling** (see paragraph 4.31).

15.30 **The current system of severity banding for project licences and the severity limits for procedures should be reviewed, particularly the use of the *moderate* category which covers a wide range of different implications for animal welfare. For the general public, the category *unclassified*, which refers to protocols and procedures involving terminally anaesthetised animals, is too vague to be informative, and should be clarified.**[5]

15.31 The *Statistics* give details about the total number of *animals* used for the first time in a year, and the total number of *procedures* initiated in that year (paragraph 13.27). As we have said, the term *procedure* refers to a wide range of activities, with very different implications for animal welfare which may arise from breeding, the withdrawal of blood, or experiments where death can be the endpoint. It is not straightforward to infer from the number of procedures undertaken how many animals have experienced what kind of pain, suffering or distress.

15.32 The humane killing of animals by means set out in Schedule 1 of the A(SP)A, for whatever purpose, is not itself a licensed procedure. Animals killed in this way are therefore not recorded in the *Statistics*. Many would argue that possession of a life is a morally relevant feature, and that it is therefore important to provide information about the number of animals that are killed humanely (paragraphs 3.47, 13.26 and 14.5).

15.33 We realise that the system of collecting data about the numbers of animals used in research is very complex and that care needs to be taken to avoid making existing administrative processes more onerous. **Nevertheless, we think it highly desirable to present clearer information about how many animals of a particular species experience pain, suffering and distress, to what degree, and for how long. We therefore recommend that the *Statistics* be revised to provide this information, including details about the number of animals killed under A(SP)A Schedule 1.**

15.34 Further thought is required to identify how changes could be made to improve information about the suffering and numbers of animals involved in research. We are aware that the APC,[6] LASA and the RSPCA together with the Boyd Group[7] are considering these issues at the time of writing. We hope that the Home Office will find our general observations useful in considering the reports from these groups.

Information about licensed research projects

15.35 There has been some discussion about whether or not, and if so to what degree, information about research projects that have been approved by the Home Office should

5 We note that some explanation can be found in the *Guidance notes* on the A(SP)A (p32). However, it is unlikely that members of the public will consult this document, and it is therefore important to clarify the terminology in appropriate places, for example in the *Statistics*.

6 The APC's Report will be available in 2005 at: http://www.apc.gov.uk/reference/reports.htm. See Animal Procedures Committee (2004) *Work Programme*, available at: http://www.apc.gov.uk/aboutapc/workprog2004.htm. Accessed on: 21 April 2005.

7 See http://www.boyd-group.demon.co.uk, see also: The Boyd Group (2004) *Categorising the severity of scientific procedures on animals - Summary and reports from three round-table discussions on the use of severity limits and bands in the UK*, available at: http://www.boyd-group.demon.co.uk/severity_report.pdf. Accessed on: 21 April 2005.

be made available to the public. We note that, following an announcement by the Government in 2004,[8] the Home Office has made available the first anonymised information in the form of *Abstracts of Project Licences*[9] in January 2005. **We welcome the principle of publishing more information, and the decision to make it available in a searchable and publicly accessible database in due course.** We also note that the information provided in the first *Abstracts* varies in content, level of detail and style of presentation. We therefore **recommend that the current form of presentation be reconsidered, to ensure that, as far as possible, meaningful information about the following categories is provided:**

- **the goals and predicted benefits of research;**
- **the probability of achieving these goals;**
- **the numbers and species of animals to be used, and an explanation of why they are needed at this stage in the project;**
- **what is likely to happen to the animals during the course of the project, including adverse effects from husbandry, supply, transport and procedures;**
- **what consideration has been given to the Three Rs to achieve all or part of the research objective(s), and how they have been applied;**
- **on what grounds possible alternatives have been rejected;**
- **source(s) of funding (i.e. public, private or both).**

15.36 Members of the Working Party were unable to agree in which form this information should be provided. While there was a range of views, those at the two ends of the spectrum were as follows:

- Some members, concurring with the views of several animal protection groups, argue that full project licences should be made available, in which only the names of researchers, research facilities and commercially sensitive information have been removed. They believe that this step would be a correct interpretation of the FoI Act (see Box 13.4), and that any further editing of licences would reduce trust in the Home Office, which might otherwise be suspected of operating in non-transparent ways. They assert that access to full, anonymised licences is necessary to allow the public to gauge the extent of costs to animals, to allow review and challenge of the information and to comment on the way in which the cost-benefit assessment has been made.[10]
- Other members, noting that their view would be shared by most researchers using animals, consider that the current format is, in principle, suitable, although they would like to see less rather than more information made public. Hence, they wish to keep the new practice under close review. They argue that the legislative framework already requires assessment of the acceptability of research by the ERP and the Home Office, and that participation by the public in the regulatory system is not permitted. This

8 Home Office (2004) *Ministerial statement announcing the outcome of the review of section 24 of the Animals (Scientific Procedures) Act 1986*, 1 July 2004, available at: http://www.homeoffice.gov.uk/docs3/animalproc_wms_section24_040701.pdf. Accessed on: 4 April 2005.

9 Home Office (2005) *Abstracts of project licences granted under the 1986 Act*, available at: http://www.homeoffice.gov.uk/docs4/abs_projectlicences0.pdf. Accessed on: 21 April 2005. The Home Office has previously released details of ten project licences under a Code of Practice which preceded the FoI, see Box 13.4.

10 See, for example, BUAV (2005) *Government in ruse to thwart Freedom of Information Act*, available at: http://www.buav.org/press/2005/01-01.htm. Accessed on: 21 April 2005; NAVS (2003) Freedom of information & animal experiments, available at: http://www.navs.org.uk/news/politics/foi.htm. Accessed on 21 April 2005.

system of assessment, together with the assessments made by the researchers themselves, and the funding bodies, is judged to be sufficient. The possibility of increased openness is viewed with scepticism because of fears about compromising accepted standards of confidentiality and commercial and academic competitiveness. Researchers using animals are also concerned that more detailed information about specific research projects could be used by militant activists to identify individuals and research facilities as potential targets.[11] They also argue that the provision of information contained in full, anonymised project licences would not be intelligible and informative to the public, and that shorter summaries would therefore be more effective in providing the public with information.

Information about the cost-benefit assessment

15.37 The common emphasis on the cost-benefit assessment in combination with the system of classification of severity bands sometimes evokes the impression that the Home Office assesses the costs and benefits of each individual experiment or procedure. As we have explained, this is not the case, since assessments take place at the much higher level of protocols and project licences (Box 13.3).[12]

15.38 The APC's 2003 Report, *Review of cost-benefit assessment in the use of animals in research*, provides very useful information about the application of the cost-benefit assessment in practice.[13] The Report also observes that relevant information is spread across several different documents, and recommends that **'there is a need for an easy-to-use, comprehensive list of factors to be taken into account in assessing costs, benefits and scientific validity, that could guide researchers and others engaged in ethical review under the act, such as members of ERPs.'**[14] **We endorse this recommendation.** Since ERPs should, ideally, also include lay people, it is important that this information is provided in a way that is accessible to non-experts. **Such a document would also be of use to the general public and the same information therefore should be provided in an accessible manner on the websites of the Home Office for the general public.** These materials should include specific case studies and also a summary of the *process* of how decisions are made in practice (see paragraph13.16 and Figure 13.1). We address further practical issues concerning the operation of the cost-benefit assessment below (paragraphs 15.54 and 15.56).

*Provision of information by campaigning organisations and researchers, and ways of improving the broader context of public debate*

Balanced information about animal research

15.39 Responses to our Consultation, and information in the press, indicate that there is still much confusion about the use of animals in research. Information which is publicly available can be unbalanced and biased. Although there are many excellent examples of responsible accounts of research involving animals, some animal protection groups sometimes use disturbing pictures that are not representative of the range of research that is permitted under current

11 News (2004) Science fears attacks will rise with Act *THES* 1657 10 September, p1.

12 See also *Guidance on the Operation of the A(SP)A 1986*, Appendix I, available at: http://www.archive.official-documents.co.uk/document/hoc/321/321-xi.htm. Accessed on: 6 May 2005.

13 The criteria for making cost-benefit assessments are discussed in Chapters 3 and 4 of the APC's report (see especially Chapter 4, Boxes 4.4, 4.5 and 4.6); A description of those involved at particular stages of processing a licence application is provided in Chapter 5. Animal Procedures Committee (2003) *Review of cost-benefit assessment in the use of animals in research*, available at: http://www.apc.gov.uk/reference/costbenefit.pdf. Accessed on: 4 April 2005.

14 Animal Procedures Committee (2003) *Review of cost-benefit assessment in the use of animals in research*, p73, available at: http://www.apc.gov.uk/reference/costbenefit.pdf. Accessed on: 4 April 2005.

regulations.[15] Equally, some of the information that is produced by organisations representing those whose work involves animals focuses disproportionately on the medical benefits of animal research, paying less attention to areas such as basic research or product testing, and the pain and suffering experienced by animals involved in such uses.[16]

15.40 We encourage animal protection groups and organisations representing those involved in research using animals to produce fair and balanced literature on this subject. This should include, among other things, detailed information about both the scientific benefits and the costs in terms of the implications for animal welfare. Similarly, the advantages and limitations of using alternative methods for research need to be discussed in a realistic manner.

15.41 Public debates about research on animals would also be enhanced by educating young people about issues raised by animal experimentation through presenting all sides of the argument. More balanced materials could make an important contribution to an improved understanding of the costs and benefits, to both humans and animals, of research involving animals, particularly for use in schools. **We therefore recommend that the UK Department for Education and Skills should commission an academic department of education that does not have close links to pressure groups or to those involved in animal research, to produce suitable materials for use across the curriculum as appropriate, especially at Key Stages 2 and 3.**

Public debates and discussions in stakeholder fora

15.42 Much can be learned from meetings which provide a forum for dialogue and allow members of the public to discuss their views with relevant experts. **We welcome provision in the Government's Science & Innovation Investment Framework 2004–2014 for a new grants scheme 'to build the capacity of citizens, the science community and policy makers to engage in the dialogue necessary to establish and maintain public confidence in making better choices about critical new areas in science and technology.'**[17] We are aware that the way the grants scheme is operated is currently being reviewed, and that Ministers may decide to allocate funding for prioritised areas. **In view of our observation about the need to improve the quality of the debate, and also the Governments discussion about animal research in the Science & Innovation Investment Framework programme,**[18] **we recommend that funding should be provided by the Government to identify and carry out novel ways of achieving stakeholder engagement and public debate on issues raised by research involving animals. The Office of Science and Technology (OST) should liaise with the APC and the NC3Rs to advise Ministers on areas of particular concern.**

15.43 However, arranging dialogue, including public debates, on controversial matters is not straightforward. For example, there was some criticism of the Government's *GM Nation?*

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15 The Advertising Standards Agency has upheld several complaints made by the RDS about the use of unrepresentative pictures in campaigns. These include rulings against Naturewatch (October 1996), Uncaged campaigns (March 1998), Save the Hillgrove Cats (August 1999), FAUNA (September 1999) and Save the Newchurch Guinea Pigs (March 2000).

16 For example, some members of the Working Party consider that information brochures such as *Medical Advances from Research using Animals* (CMP 2003/4), *Animal Research and Human Medicine* (ABPI 2004) or *The Use of Non-human Animals in Research: A guide for scientists* (Royal Society, 2003), available at: http://www.royalsoc.ac.uk/policy/AnimalsResearch.htm Accessed on: 21 April 2005, which are intended to provide neutral information about animal research, are insufficiently balanced. See also Russell WMS (2004) The use of non-human animals in research: a guide for scientists *ATLA* **32**: 119–20.

17 See HM Treasury/DTI/Department for education and skills (2004) *Science & Innovation Investment Framework 2004-2014*, paragraph 21, available at: http://www.hm-treasury.gov.uk/media/33A/AB/spend04_sciencedoc_1_090704.pdf. Accessed on: 21 April 2005.

18 See HM Treasury/DTI/Department for education and skills (2004) *Science & Innovation Investment Framework 2004-2014*, paragraph 6.16-7.20, available at: http://www.hm-treasury.gov.uk/media/33A/AB/spend04_sciencedoc_1_090704.pdf. Accessed on: 21 April 2005.

debate which was organised in 2003.[19] There are a number of different approaches to be considered, from large public meetings to consensus conferences and citizens' juries. While we do not give detailed attention as to which approach might be best suited to discussion of issues raised by animal research we make some general observations.

15.44 First, it is important to create an environment for debate in which all views are heard and all participants are treated with the same respect. Secondly, the purpose and outcome of any public meeting or debate needs to be clear from the outset. For example, it might need to be stated whether the purpose is restricted to stimulating exchange of views, or whether it is being undertaken in the context of informing decision-making processes. Failure to consider the appropriate approach and outcome of any such exercise can possibly lead to more, rather than less, polarisation as well as to increasing scepticism about public-engagement exercises and trust in democratic processes.

15.45 In addition to public events, there are a number of *ad hoc* and permanent stakeholder groups that enable discussion among stakeholders. In our own debates, we realised the importance of having members who between them represent a broad spectrum of views on research involving animals. This approach allowed for comprehensive consideration of relevant arguments about specific areas of research. We encourage all parties to continue to take part in such fora.

Research on views of the public

15.46 We have already commented on the limitations of opinion polls, and the scarcity of peer-reviewed academic research, which could help provide reliable assessments to be made about the views of members of the public about research involving animals (paragraphs 1.14–1.16). Such information can be important in considering whether or not policies are likely to be supported by the majority of the population. **We therefore recommend that the Economic and Social Research Council (ESRC) and other relevant funding bodies provide funding for research to be undertaken on the knowledge, opinions and views of members of the public on animal research, and their underlying ways of reasoning.** Particular attention should be paid to the level and quality of information that participants have prior to, and while taking part in, the research, and to the ways in which provision of information affects individual responses.

Violence and intimidation

15.47 The current climate in which animal research takes place has been influenced by several factors, including protests that often entail threats, harassment and violence (paragraphs 2.22–2.24). The effects of these actions have been highly disproportionate to the very small number of activists involved.[20]

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19 Environment, Food and Rural Affairs Committee (2003) *Eighteenth Report*, available at: http://www.publications.parliament.uk/pa/cm200203/cmselect/cmenvfru/1220/122002.htm. Accessed on: 21 April 2005; Understanding Risk Team, University of East Anglia (2004) *A Deliberative Future? An Independent Evaluation of the GM Nation? Public Debate about the Possible Commercialisation of Transgenic Crops in Britain, 2003, Working Paper 04-02, University of East Anglia*, available at: http://www.uea.ac.uk/env/pur/latest_news.html. Accessed on: 21 April 2005.

20 Militant extremists have brought considerable fear to the lives of those whose work involves research on animals, and to their families. Many people who do not have direct association with animal laboratories but who work for institutions that provide services that facilitate animal experimentation have also been affected. Similarly, several charities which fund research involving animals have stated that they do not wish to engage in an open dialogue about the legitimacy of research on animals for fear of becoming a target for extremists. Animal rights extremists threaten not only scientists engaged directly in research, but also those working for legitimate animal welfare organizations such as the RSPCA and professional bodies such as the IAT and LASA. For example, for the past four years, the IAT has not been able to hold its annual conference in the UK because of threats from extremists. LASA has also had to hold all its meetings in undisclosed locations to minimise the attention of militant protestors. See also Home Office/DTI (2004) *Animal Welfare – Human Rights: protecting people from animal rights extremists*, available at: http://www.homeoffice.gov.uk/docs3/humanrights.pdf. Accessed on: 21 April 2005.

15.48 It is tempting to dismiss animal rights extremism as being wholly unwarranted. Yet those who resort to violence maintain they have the moral high ground. This can be frustrating to those who campaign within strictly constitutional limits, and who fear that violent and abusive actions damage their legitimate cause. Those who promote violence and intimidation to pursue their case against animal research often attempt to justify their actions on the basis that they are liberating animals in much the same way as the Allies liberated Europe from the Nazis. They believe the democratic process is too slow, and moreover that the voting system is invalid, in that animals are disenfranchised. In the wake of their activities are others who would not themselves use violence but who are prepared to threaten it, persuading themselves that bullying is acceptable because it is aimed at people who are bullying animals.

15.49 If some of those engaged in the animal rights movement were able to force research abroad or prevent multinational companies from opting to conduct work in the UK, by means of militant actions, they would claim such outcomes as a victory.[21] During our fact-finding meetings we heard different accounts of the effects of the actions of groups involved. Some of those working in the pharmaceutical industry and the contract research sector said that the presence of animal rights extremism was not a major factor in considering whether or not to opt for a different research location. But there have also been reports to the opposite effect, and attention has been drawn to possible economic and scientific setbacks for the UK, should protestors be able to continue their activities.[22] In 2004, multinational companies repeatedly urged the UK Government to amend the legal framework applicable to animal rights-related extremism, emphasising that the *status quo* was unacceptable and might influence decisions about investment. In 2005 the UK Government responded by making amendments to the Serious Organised Crime and Police Bill.[23]

15.50 **We conclude that all approaches based on violence and intimidation are morally wrong:** democracy is a precious achievement that allows conflict to be resolved without recourse to violence. It cannot permit exceptions where militant activities displace debate and consensus, otherwise anyone with any strongly held view would be able to prevail over the majority. The debate about animal experimentation must be conducted in a reasonable and civilised manner. Seeking to force research out of the country is not a solution to the complex issues it raises. We therefore fully concur on the issue of militant protest with one of the leading animal rights advocates, Professor Peter Singer:

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21 See, for example the Initiative *Gateway to Hell*, available at: http://www.gatewaytohell.net. Accessed on April 21 2005.

22 According to the ABPI, more than 65,000 people are directly employed by the pharmaceutical sector and a further 250,000 are dependent on it for their employment. In 2003, the industry contributed £2bn to the UK economy and generated exports of £7bn and a trade surplus of £2.3bn, the third highest after power generation and oil products. Members of the ABPI spend a combined £30–70 million a year on security, see Hennock M (2004) Pharma firms take on the extremists *BBC News online*, available at: http://news.bbc.co.uk/1/hi/business/3933939.stm. Accessed on 21 April 2005; Evans M (2004) Extremist animal rights activists pose main threat to economy *The Times online*, available at: http://www.timesonline.co.uk/article/0,,2-1396891,00.html. Accessed on 21 April 2005.

23 The Bill received Royal assent on 11 April 2005 and thus became the Serious Organised Crime and Police Act 2005, available at: http://www.uk-legislation.hmso.gov.uk/acts/acts2005/20050015.htm. Accessed on: 5 May. Sections 145–149 make it a criminal offence to cause 'economic damage' by means of organised campaigns of intimidation. They are intended to improve the enforcement of legal sanctions of attacks against businesses, company employees and their family members, charity shops and universities. In addition to other measures in the Act, new offences are introduced to respond to typical forms of protests. These include a new offence of protesting outside someone's home in such a way that causes harassment, alarm or distress to residents. There are additional powers for a constable to direct a protestor to leave the vicinity of a home and not return within such period as the constable may specify, up to three months. Individuals guilty of an offence under section 142 or 143 are liable, on summary conviction, to imprisonment for a term not exceeding 12 months or to a fine not exceeding the statutory maximum, or to both, on conviction on indictment, to imprisonment for a term not exceeding five years or to a fine, or to both. Since these provisions were agreed after the final meeting of the Working Party, we do not comment on the appropriateness of the Act, although in principle we welcome regulations seeking to prevent harassment and intimidation.

> 'I cannot support the use of violence in the cause of animal liberation. It sets a dangerous precedent – or, one might say, it follows dangerous precedents. In the United States, 'pro-life' extremists have fire-bombed abortion clinics and murdered doctors who terminate pregnancies. I consider these defenders of the sanctity of human life from conception to be misguided; but no doubt they are just as sincere in their convictions as defenders of animals. It is difficult to find democratic principles that would allow one group to use intimidation and violence, and deny the same methods to the other.'[24]

Open laboratories

15.51 In a highly polarised debate where many people hold strong views, the only option for making progress is for all concerned to engage in debate fairly and respectfully. Members of the public should have the opportunity to discuss animal experiments with researchers, and to visit laboratories to see the facilities and the animals that are being used. We realise that this suggestion raises a number of practical issues. It would be unacceptable if visitors to laboratory facilities abused the opportunity by protesting against research involving animals, using argumentative or unruly behaviour or by gathering intelligence so as to cause damage to property or harm to staff. Laboratories need to ensure that visitors have no such aims. Measures are also needed to prevent the exposure of visitors to allergens and to ensure that they do not disturb animals or spread infections.

15.52 Despite these possible problems, and the fears of members of the research community of being targeted by militant protestors, some academic and industrial scientists and scientific institutions involved in animal research are willing to engage with the public (see paragraph 2.30). Others are reluctant to do so. The Working Party experienced the fragile climate of trust at first hand, as it was not possible for all members who wished to attend fact-finding meetings at research facilities to do so (see Appendix 4). We take the view that in order to improve and sustain public trust, researchers at animal research facilities must find more ways to open themselves to dialogue. **We therefore recommend that those involved in animal experimentation should take a proactive stance with regard to explaining their research, the reasons for conducting it, the actual implications for the animals involved and the beneficial outcomes they intend for society.** These discussions should take the form of a two-way process, in which scientists not only inform the public about their research, but also listen to and understand concerns by members of the public.

***The role of legislation and regulation***

15.53 We learned from some of our discussions with representatives of patient groups that reference frequently is being made to the provisions of the A(SP)A, so as to allay concerns by members and non-members about animal research. Whether or not such referrals are suitable for the purpose depends not only on the formal provisions of the law, but also on its application in practice. Many animal protection organisations and respondents to the Consultation expressed concerns about the implementation of the provisions of the A(SP)A and quoted what they believed to be examples of ineffective regulation.[25] In contrast, many members of the research community who submitted comments were concerned about

24 Singer P (2004) Humans are sentient too *The Guardian* 30 July, p21.

25 Those critical of the implementation of the A(SP)A point to a number of reports which draw attention to claimed inadequacies in the implementation of the A(SP)A and they emphasise that the House of Lords Report concluded that the Home Office Inspectorate should be subject to periodic review, by a body other than the Inspectorate itself. See House of Lords Select Committee (2002) *Animals in Scientific Procedures* (Norwich: TSO), paragraph 5.13, Chapter 2, Box 2.9, and Lyons D (2004) *In a collapsed state – Imutran xenotransplantation research: a case study of Home Office enforcement of animal experimentation legislation, Uncaged campaigns*, available at: http://www.uncaged.co.uk/. Accessed on 21 April 2005.

what they perceived to be overly detailed and burdensome regulation.[26] A thorough review of regulation is beyond the scope of this Report and is being considered by other bodies.[27] Nonetheless, we offer some general observations below.[28]

*Cost-benefit assessment and moral agency*

15.54 The cost-benefit assessment is at the heart of the regulation of research on animals in the UK. There is sometimes the view that the assessment is only being carried out by the Home Office, which 'tells the researchers what to do' once it has decided on whether or not a licence application fulfils the criteria of the A(SP)A and is thus, from the regulator's point of view, acceptable. The APC's 2003 Report *Review of cost-benefit assessment in the use of animals in research* observed that this interpretation would be simplistic, since other individuals and committees are involved in assessing directly or indirectly the costs and benefits of a project (paragraph 13.16). The APC therefore emphasised that:

> 'project licence holders and others involved in study design and initiation bear responsibility for clearly setting out the costs and benefits of their research and carrying out cost-benefit assessments of their work, including critical evaluation of the need for animal studies at all. The roles of other bodies, such as the Home Office, ERP, and, where relevant, APC, are to evaluate, advise, and in some cases adjudicate the researchers' own cost-benefit assessments.'[29]

15.55 We welcome this clarification, which is compatible with our discussion about moral agency (paragraph 3.69). As we have said, it would be wrong to perceive acting morally simply as following rules. Instead, active and continued scrutiny of the costs and benefits is required from all those involved, before, during and after research. This responsibility cannot be devolved to regulators, and, as the APC has emphasised, the system is not intended to function in this way.

15.56 The APC's clarification underlines the importance of clear guidance on how to make cost-benefit assessments. Furthermore, it implies that both funding bodies and peer reviewers who may be involved in assessing licence applications have to take their responsibilities in the review process seriously. **We recommend that those involved in reviewing research proposals** (see Figure 13.1) **at every stage prior to submission to the Home Office consider not only the scientific aspects, but also animal welfare in appropriate detail**. Good science and good animal welfare are closely interrelated, and it would be wrong for the scientific review process to ignore animal welfare issues. We are aware that many funding bodies recognise this fact. In addition to assessments by internal review boards, some, such as the Wellcome Trust and the MRC routinely invite external reviewers to comment on welfare issues and the way the Three Rs are considered in research proposals involving the use of

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26 In support of claims that the implementation of the A(SP)A leads to excessive bureaucracy, researchers involved in animal experimentation have drawn attention to a number of recent reports including the House of Lords Select Committee Report, which concluded that 'The UK should strive not for the tightest regulation, but for the best regulation, properly enforced', They have also highlighted several recommendations made in this area by the Select Committee including the simplifying and shortening of project licences forms, and allowing the ERP to have the authority to approve routine or minor amendments. see House of Lords Select Committee (2002) *Animals in Scientific Procedures* (Norwich: TSO), paragraphs 5.33, 5.40, 6.11; Expert Group on Efficient Regulation (2001) *The Regulation of the Use of Animals in Scientific Procedures* (London).

27 See, for example, Reports by the APC (available at: http://www.apc.gov.uk), or the Boyd Group (available at: http://www.boyd-group.demon.co.uk).

28 Issues arising from different legislative and regulatory requirements in other countries, and problems in harmonising guidance internationally are discussed in paragraphs 15.84-15.91.

29 Animal Procedures Committee (2003) *Review of cost-benefit assessment in the use of animals in research*, p77, available at: http://www.apc.gov.uk/reference/costbenefit.pdf. Accessed on: 4 Apr 2005.

animals. However, **there is anecdotal evidence that this practice is not universal, and we recommend that other funding bodies review their approach**.

***Development and implementation of the Three Rs***

15.57 We have observed that the Three Rs have a crucial role in the ethical justification of research. With regard to Replacements we concluded that it is necessary to ask the question of why Replacements in specific research areas are not available, and what is required to make them so (paragraph 3.63 and 11.19–11.30). A slightly different situation prevails with regard to Refinement and Reduction in that relevant information about these strategies exists in many areas, but their use and application is not sufficiently widespread. We referred to research showing that there is some variance in the application of Refinement,[30] and we also identified possible barriers, highlighting scientific, regulatory, organisational, and resource factors (paragraphs 12.23–12.28), all of which can have impact on the implementation of Refinement methods. Below we present our conclusions and recommendations with regard to improving the application of the Three Rs.

*Publishing information about the Three Rs*

15.58 Many members of the research community emphasise that, wherever possible, they implement the Three Rs, often exceeding regulatory requirements. In some cases, advances are made by individual researchers, but knowledge of improved practices tends to be limited to colleagues in the research establishment, and may not always be disseminated nationally or internationally in a systematic manner. In order to improve knowledge about and awareness of the Three Rs **we recommend that all journals publishing results of research involving animals consider the inclusion of a category on the Three Rs in the methodology section**.[31] Many journals now also provide supplementary information for articles on websites, and details about the implementation on Three Rs could be provided in this way.

*Coordination of efforts between funding bodies and the NC3Rs*

15.59 Medical research charities and research councils fund a large amount of animal research and should be encouraged to take more responsibility for the promotion and implementation of the Three Rs. Further to recommending that external reviewers comment on the way the Three Rs have been implemented in funding proposals (paragraph 15.56), we consider that those who fund research have two additional responsibilities. **First, in order to improve a systematic application of the Three Rs, funding bodies should request that for each project that receives funding, a short summary be submitted to the NC3Rs which describes the way in which the Three Rs were implemented in the project, which obstacles were encountered and how they might be overcome in the future.** This information would be useful to the NC3Rs in promoting exchange of experience and fostering best practice. **Secondly, based on this information, and in consultation with the NC3Rs, funding bodies should encourage funding applications for Three R-related research in areas that pose challenges.**

*Enhancing the role of the Ethical Review Process (ERP)*

30 See Richardson CA, Flecknell PA (2005) Anaesthesia and Post-operative Analgesia Following Experimental Surgery in Laboratory Rodents: Are we making Progress? *ATLA* **33**: 119–127; paragraph 12.26.

31 In a different context, one journal has recently reviewed its policy on the provision of information about statistical methodology in published articles. Research had revealed that this information was of varying quality, and the editors therefore decided to introduce a requirement for authors to submit specific information about statistical methods used in the methodology section of each article, see Editorial (2005) Statistically significant *Nat Med* **11**: 1-1.

15.60 The ERP has the potential to make a greater contribution to the identification, promotion and implementation of the Three Rs and could play a more proactive role in identifying best practice and helping to facilitate exchange of information. When the ERP was established in 1999, one of its main objectives was to promote the application of the Three Rs (see paragraph 13.23). However, in practice, many ERPs focus on the review of licence applications, and although this includes consideration of the Three Rs in relation to the specific project, there is potential for a more general contribution. For example, some ERPs have dedicated Three Rs groups that review husbandry and procedural issues. We acknowledge that some organisations, particularly the LASA and the RSPCA, have organised meetings for ERP members in the past to assist this process. We support this approach and **recommend that these two organisations, together with other stakeholders where appropriate, identify a systematic and sustainable strategy to ensure that the ERP contributes most effectively to developing best practice in the Three Rs**.

Examination of new technologies for Three R potential: Chair of the Three Rs

15.61 We have described the complex interplay leading to the development of Replacements in Chapter 11. Strategic examination of new scientific technologies for Replacement potential, their adaptation for general use and transfer of the technology could help to ensure further progress. Scientists working in basic research who develop new methods for specific research questions often do not have the Refinement, Reduction or Replacement of animal experiments as their main objective and tend not to adapt or promote new methods for this purpose. Much more 'horizon scanning' is needed. The Working Party has therefore considered whether it would be useful to institute at least one Chair of the Three Rs, to undertake research on new technologies for Refinement, Reduction and Replacement potential and to encourage students to carry out research with an emphasis on alternative methods. Several issues would need to be assessed in more detail before such a proposal could be developed further. First, the relationship of the Chair to existing initiatives and organisations that seek to promote the Three Rs would need to be clarified, to avoid duplication of effort, and to ensure that funds to promote the Three Rs are spent most effectively. Secondly, the exact profile of the Chair would need to be carefully defined, to assess whether it would be more appropriate to focus the review of the wide range of new technologies in different areas of research on one of the Three Rs only, for example on Replacement. We have therefore not been able to agree on whether or not a Chair would advance and contribute to increased implementation of the Three Rs. However, **we consider that it would be of value if the MRC, the Wellcome Trust and other major funders of research, in consultation with the NC3Rs, review and explore further the proposal of establishing and funding such a Chair**.

*Thorough analysis of scientific barriers to Replacements*

15.62 We have considered in Chapter 11 a range of different barriers to Replacements, including regulatory, organisational and resource constraints (paragraphs 11.19–11.30). These difficulties are sometimes cited to dismiss further consideration of Replacement as unfeasible, regardless of the exact objectives of a particular research project. We also observed that some of those opposed to research involving animals claim that a far wider range of research than is commonly assumed could be replaced by alternative non-animal methods, if there was sufficient will to do so (paragraph 11.3). In order to make further progress in the development and the implementation of Replacements, and in order to address the range of associated expectations it would be desirable to undertake a thorough analysis of the scientific barriers to Replacement and how they might be overcome. This task cannot be addressed in general terms, but requires an in-depth analysis of specific projects

in particular areas of research. Since the unavailability of non-animal methods plays a central role in the cost-benefit assessment carried out under the A(SP)A,[32] **we recommend that Ministers request the APC to undertake or commission such an analysis for a series of projects with a wide range of scientific objectives**. A clear exposition of obstacles, and strategies for overcoming them would, first, allow research efforts to be focused on problems that must be overcome if animals are to be replaced for a particular purpose. Secondly, such an analysis would identify publicly the scientific problems which are thought to be insurmountable.

***Other issues***

15.63 In this section we consider a number of more specific issues:

- ways of motivating and monitoring the reduction of research involving animals (paragraphs 15.65–15.67);
- ways of avoiding duplication of research (paragraphs 15.68–15.70);
- issues raised by the use of GM animals in basic research (paragraphs 15.71–15.75);
- the scientific validity of animal research and the use of animals in the study of human disease (paragraphs 15.76–15.80);
- toxicity testing (paragraphs 15.81–15.83); and
- the international context of research involving animals (paragraphs 15.84–15.91).

*Motivating and monitoring the reduction of animal research*

15.64 One way of motivating and monitoring any proposed reduction of animal experiments would be to set *targets*. The most radical form of target would be to aim to abandon or phase out a specific area of animal experimentation. As we have said, in the UK the Home Office announced in 1998 that it would not issue any new licences for testing cosmetic products, for the testing of alcohol or tobacco products or for research involving the great apes.[33] More recently, a 7th Amendment to the EU Cosmetics Directive has been approved, which will impose a marketing and sales ban in the EU on cosmetics that have been tested on animals, effective from March 2005.

15.65 Members of the Working Party disagree about the setting of targets. Those who favoured the approach argued that without targets there tends to be drift and fatalism. They emphasised the following:

- Setting targets can focus the mind and encourage determined action. As a heuristic device, the explicit setting of targets can be useful in helping to decide where and how reductions might be achieved.
- The setting of targets is routine in industry, academia and public institutions. It is generally regarded as an essential mechanism to bring about change, and to measure and monitor progress.
- By establishing deadlines, targets can encourage greater and more strategic collaboration in developing alternatives.

32 A(SP)A, Section 5 (a).

33 Animal Procedures Committee (1998) *Press release: Government Announces End To Cosmetic Testing On Animals*, available at: http://www.apc.gov.uk/press_releases/981126b.htm. Accessed on: 1 Apr 2005.

- Ambitious targets might result in the faster development of alternatives, and could establish a country (such as the UK) as a world leader in this area.

15.66 Those who have major reservations with regard to the setting of targets question the feasibility of the approach and assert that those accountable can be unfairly held responsible for unrealistic expectations. Accordingly they consider the following:

- There may be scientific limitations on what can be achieved without using animals in specific areas of research: hence, while setting targets may be feasible in areas such as cosmetics testing, it may be far more difficult in other areas, especially in basic research.
- There may be also pragmatic difficulties, especially in areas such as basic research, and many questions would have to be addressed. For example, how would the demand for and use of animals by the many different research groups be assessed? If there were support for a gross target (such as 'reduce the number of animal X by 70 percent by year Y', how would such a decision be implemented? How many animals could be used by particular commercial laboratories during that period, and how many by academic researchers? How would different capacities of coping with possible higher costs of implementing Replacement methods be considered in the process?
- There can be no guarantee that targets can be met in all instances: difficulties can arise in the case of sudden emergencies, such as the BSE crisis, which might require an unexpected increase in the use of animals.
- Setting targets could lead to alternatives being introduced too rapidly, before they have been subject to rigorous scientific assessment. This could have damaging implications for progress in scientific research and the protection of human and animal health or the environment, as well as for the credibility of alternative methods.
- If targets are set unilaterally, for example in one country, the research or testing may be exported to other countries.

15.67 We make the following observations:

- We welcome the concept of targets as a useful and universally used means of measuring progress towards specific aims. But we also see problems in applying such a strategy to research involving animals, where, in many cases, the setting of specific quantitative (numerical) targets is felt by researchers using animals to be unhelpful. Instead, we suggest that reduction could be encouraged and monitored by means of a more flexible approach. One way would be to consider qualitative *markers of reduction*, for example, aimed at reducing research that causes substantial suffering. **The Government's Interdepartmental Group on the Three Rs should undertake or commission a feasibility study to identify which kinds of *reduction markers* could be set in particular areas of applied and/or basic research.**
- In principle, reduction markers should only be set if they can be linked to a realistic strategy for developing the necessary Replacement methods that will not compromise the amount and quality of basic and applied biomedical research and testing that would otherwise be licensed by the Home Office. Reduction markers that 'ration discovery' are not compatible with the scientific approach.
- The development of any strategy should primarily be the responsibility of legislative bodies and governments, as should the task of providing the infrastructure and some of the funding to facilitate the process, in close consultation with stakeholders from academia, industry and animal protection groups.
- In implementing reduction markers it is crucial that initiatives at the national level are complemented, although not limited by, initiatives at the international level.

*Duplication*

15.68 Another area where there may be potential for reduction concerns the avoidance of duplication of research or testing (see paragraphs 12.6 and 15.16). In some areas, this can be achieved simply by better coordination and dissemination of information. For example, a recent report by the European Commission on the *Evaluation of the Active Substances of Plant Protection Products*[34] observed:

> '4.6 … multiple dossiers. Many different dossiers were submitted for the same substances, unnecessarily multiplying the number of evaluations required. While every effort was made to encourage notifiers to create taskforces and to submit a single dossier per substance, it was not always possible to achieve this. For example, there were 35 notifiers for the active substance glyphosate and 11 dossiers were submitted. This proved wasteful of resources, as the Rapporteur Member State (Germany) had to examine each one. In the event, only four dossiers were considered complete and could be assessed in detail. Ideally, there would have been a single dossier. This would have saved resources both for the various notifiers and for the Rapporteur Member State. It would also have resulted in fewer laboratory animals being sacrificed in duplicated testing. While every effort is still being made to encourage notifiers to create taskforces and to submit a single dossier per substance, it is still not always possible to achieve this. A solution could be to introduce provision in the legislation to avoid duplicate testing e.g. action point 5F in the White Paper on a Chemicals Strategy[35] proposes that any duplicate testing on vertebrate animals will not result in an exemption from the duty to reimburse the party that owns the property rights to the first test.'

15.69 While this is a clear and unfortunate example of duplication, it appears that the extent to which duplication occurs, whether internationally or nationally, is difficult to assess. Those suspecting that there is a substantial and avoidable amount of duplication are concerned that academic and commercial competition and the aim of protecting intellectual property rights frequently lead researchers to be reluctant to share data. They also assert that many more examples of insufficient coordination, similar to the one described above, could be given.[36] Those who disagree consider that in general there are sufficient mechanisms in place to ensure the avoidance of duplication, such as the publication of peer-reviewed research in scientific journals and presentation at conferences. They take the view that duplication is unlikely to be a widespread phenomenon because funding bodies only support novel research and because both academic and commercial research institutes need to manage resources efficiently, usually implying that only original research is carried out.

15.70 We cannot explore the question of the extent to which duplication occurs, or the feasibility of devising mechanisms that help to avoid the duplication of research in this Report. But we are clear that, in principle, duplication is unacceptable (paragraph 15.16) and we therefore welcome the approach underlying the UK Government's Inter-Departmental Data Sharing Concordat (paragraph 12.6). The Concordat has recently been reviewed by the Government who commented that the agreement had ensured that 'regulators promote data sharing within the scientific community', noting also that there was no

34 Services of the European Commission (2001) *Technical Annex to Report from the Commission to the European Parliament and the Council on the Evaluation of the active substances of plant protection products, SANCO/2692/2001 of 25 July 2001*, available at: http://europa.eu.int/comm/food/plant/protection/resources/ppp01_ann_en.pdf. Accessed on: 21 Apr 2005.

35 European Commission (2001) *White Paper: Strategy for a future chemicals policy. COM (2001)88 final of 27.2.2001* (Brussels: EC).

36 See, for example: British Union for the Abolition of Vivisection (2004) *Memorandum from the British Union for the Abolition of Vivisection, submission to the Select Committee on Science and Technology*, available at: http://www.publications.parliament.uk/pa/cm200304/cmselect/cmsctech/172/172we20.htm. Accessed on 21 April 2005.

evidence that duplication was 'a significant problem in the UK.'[37] The Working Party has not been able to study the review, and is hence not in a position to comment on the Government's view.[38] We note that the APC welcomed the Concordat in its 2003 Report *Review of Cost Benefit Assessment in the Use of Animal Research*[39] but cautioned that it is not yet clear how effective it will be in preventing duplication of animal studies. In particular, the APC was concerned about the voluntary nature of the Concordat, and considered whether more binding measures, such as legislation, will be needed to achieve the Concordat's aims. **We endorse the APC's conclusion that the operation and effectiveness of the Concordat should be monitored carefully and reports placed in the public domain.** The Concordat will be reviewed again in 2006. Depending on the outcome of the review, Ministers should explore whether it would be useful to request the APC to undertake a systematic study addressing in more detail specific issues raised by the possible duplication of research. Such a study could complement and develop further the review of the Concordat, for example by assessing the extent of the problem and, where appropriate, identifying strategies for the avoidance of duplication nationally and internationally. Consideration could also be given to the question of whether duplication occurs because some kinds of data are not made publicly available when experiments fail. It would be especially undesirable if researchers wasted time and effort in duplicating experiments that have elsewhere been found to be unsuccessful. The study could also consider whether funding bodies would have a role in sharing or making available information about past or current research, in order to avoid duplication. We consider special issues with regard to avoiding duplication in the case of GM animals in the next section.

*The use of GM animals in basic research*

15.71 Specific problems in assessing welfare may be raised by relatively novel ways of producing animals, such as genetic modification or cloning. We take the view that the focus of any concern, in the case of all deliberate attempts to influence the genetic basis of animals, should be on the welfare implications in terms of the likely pain, suffering or distress.

15.72 Welfare implications that may be associated with specific ways of producing animals should be assessed as far as possible in advance. In some areas of basic research, such as forward or reverse genetics, welfare assessments are often not straightforward. If such research is deemed desirable, it is important to limit the number of animals produced as far as possible, for example by ensuring good coordination within and between different laboratories and countries. This is especially so in view of estimates that over the next two decades 300,000 new genetic lines of mice could be created, and expectations that the total number of mice that are expected to be used in mutagenesis and phenotyping studies are of the order of several million each year in the UK alone. We also observed that large numbers of animals are used to produce and maintain each line of GM animals (see paragraphs 5.22 and 7.5).

37 Home Office (2005) *Ministerial Response on the Report by the Animals Procedures Committee – Review of Cost Benefit Assessment in the use of animals in research*, p10, available at: http://www.homeoffice.gov.uk/docs4/jw280305flint_banner_report_by_the_animal_procedures_committee.pdf. Accessed on: 21 April 2005.

38 Parliamentary Under Secretary of State Caroline Flint commented in the Government's response of 28 March 2005 to the APC's Report on the cost-benefit assessment that 'the outcome of the review' would be published as an Annex to the Minutes of the Inter-Departmental Group on the Three Rs, see Home Office (2005) *op. cit.* However, the Working Party was not able to consider this document before finalising this Report.

39 Animal Procedures Committee (2003) *Review of cost-benefit assessment in the use of animals in research*, p52, available at: http://www.apc.gov.uk/reference/costbenefit.pdf. Accessed on: 4 April 2005.

15.73 Documentation of the phenotypic outcomes of genetic modification (i.e. documentation about the way in which animals are affected) can facilitate the future monitoring and assessment of welfare implications experienced by animals produced in the context of forward or reverse genetics (paragraphs 5.18–5.21). A systematic approach to the description of GM phenotypes is crucial for assessing and monitoring welfare implications, and for undertaking thorough cost-benefit assessments. For this reason, **we recommend that more efforts should be made to establish comprehensive ontologies**[40] **in the form of databases for GM animals. These databases should not be restricted to the receipt and dissemination of phenotypic information relevant to the scientific objectives of the research, but should also provide detailed description of associated implications for welfare. Established central databases, such as the Mouse Genome Database (MGD) in the USA,**[41] **should be used as the primary mechanism for archiving and distributing information on GM animals**. The information should be made available on freely accessible websites for the use of the scientific community and interested lay people.

15.74 It is also important to continue to investigate and improve current methods for assessing the phenotypic and welfare status of GM animals. Any terminology and ontology for describing specific welfare implications should be integrated with the emerging phenotype ontologies. We note that current welfare assessment systems vary with regard to the amount of information and the degree of detail being made available.[42] **We recommend that the NC3Rs should consider this variation with a view to advising on the rationalisation and development of phenotype and welfare ontologies and their interrelationships.**

15.75 **We also recommend that scientific journals require the submission of phenotype and associated data about welfare to databases as a condition of acceptance of submitted papers.** Although scientists often routinely submit information about new phenotypes to databases such as MGD, a more systematic approach would be useful in promoting the availability of information about both the phenotype and the implications for welfare, which would help avoid duplication and improve welfare management. Data should be provided according to the requirements of the standardised transgenic mouse nomenclature.[43]

*The scientific validity of animal research and the use of animals in the study of human disease*

15.76 In Chapters 5-8 we gave a number of examples which illustrated the use of animals as models for human diseases, and for the assessment of effective and safe interventions. We also considered claims about the predictability and transferability of animal experimentation (paragraphs 8.37–8.41, 8.43 and 10.27–10.43) and concurred with the APC that, because of relevant similarities of anatomical, physiological and neurological structures the scientific validity of animal experiments is:

> 'a condition capable of being fulfilled, but has to be judged case by case and subjected to detailed critical evaluation.'[44]

40 An 'ontology' in this context is an explicit formal specification of terms and the relationships among them, used to underpin the construction and querying of databases.

41 See *Mouse Genome Informatics (MGI)*, available at: http://www.informatics.jax.org. Accessed on: 21 Apr 2005.

42 Jegstrup I, Thon R *et al*. (2004) Characterization of transgenic mice - a comparison of protocols for welfare evaluation and phenotype characterization of mice with a suggestion on a future certificate of instruction *Lab Anim* **37**: p1-9.

43 See *Mouse Nomenclature Home Page*, available at: http://www.informatics.jax.org/mgihome//nomen/index.shtml. Accessed on 21 April 2005.

44 Animal Procedures Committee (2003) *Review of cost-benefit assessment in the use of animals in research*, p26, available at: http://www.apc.gov.uk/reference/costbenefit.pdf. Accessed on: 4 April 2005.

15.77 The question about the scientific validity of animal experimentation for medical purposes is often confused with questions about complex ethical issues. We emphasised in Chapter 3 that the separation of scientific and ethical questions is essential if greater clarity is to be achieved in the debate about research involving animals. We observed that there is a relatively limited number of useful reviews currently available (paragraph 10.46). **In principle, it would therefore be desirable to undertake further systematic reviews and meta-analyses to evaluate more fully the predictability and transferability of animal models** (see paragraph 10.39). We are aware that carrying out such reviews may be complicated by a number of problems.

15.78 First, it may be difficult to assess if an animal experiment failed to yield specific data because the wrong animal model was used or because the study design was flawed. Any proposed review should identify clearly whether there are areas of research in which scientific methodology (for example, statistical analysis) needs to be improved, or whether there is reason to question the scientific validity of using specific animals as models in particular areas of research.

15.79 Secondly, care should be taken when selecting the studies that are analysed in any review, and the reasons for selection must be made explicit to avoid misunderstandings. Problems could arise if, for example, a review focuses exclusively on an area where progress has been difficult, as the results might be interpreted by some as suggesting that animal research *in general* yields insufficiently transferable results. Similarly, reviews that focus exclusively on areas where progress has been relatively straightforward might be interpreted as proof that *all* animal research yields useful and directly applicable results. Clearly, such interpretations are not useful and contrary to the evidence presented in Chapters 5–9.

15.80 On balance, we consider that there is merit in undertaking appropriately designed and presented reviews on the scientific validity of animal research in specific areas. Since the scientific evaluation of animal research is fundamental to the cost-benefit assessment of any research, **we recommend that the Home Office, in collaboration with major funders of research such as the Wellcome Trust, the MRC, the BBSRC, animal protection groups and industry associations such as the ABPI, should consider ways of funding and carrying out these reviews. In devising a strategy, priorities should be identified which, in order to respond to concerns of the public, consider, among other things, the validity of research that falls in the substantial category, and research that involves primates**.

*Testing for toxicity*

15.81 Current trends in society suggest that there is an increasing intolerance to risk, although some commentators believe we are now over-zealous in testing requirements.[45] We described the types of procedures typically undertaken in toxicology research in paragraphs 9.9–9.25. In view of the severity that some toxicity testing can entail, **we endorse the recommendation of the House of Lords Select Committee *Report on Animals in Scientific Procedures* (2002) that 'the government and the scientific community should engage more in a systematic and visible search for methods involving the Three Rs in toxicology. The Government should nominate one department to take the lead in this.' We recommend that the Inter-Departmental Group on the Three Rs should coordinate this work**.

15.82 With regard to international initiatives the Working Party is concerned about the potential impact of recent EU legislation for new and existing chemicals testing (REACH), which is likely to be implemented by 2006. According to some estimates, had the initial proposal been implemented, up to 12.8 million animals could have been involved for the testing of

45 For example, Durodie B (2003) The true cost of precautionary chemicals regulation *Risk Anal* **23**(2): 389–98.

approximately 30,000 existing chemicals (see Box 9.2).[46] The conclusion that the scale of testing and use of animals did not appear to justify the additional protection afforded to society has been widely supported, and discussions about the actual implementation were still in progress at the time of writing. Whatever its final form, REACH will greatly increase animal testing across the EU. While we make no detailed recommendation in this area, it is crucial that new approaches to risk assessment that implement the Three Rs most effectively should be explored, particularly by making maximum use of data sharing (paragraphs 15.68 and 15.70), and using computational and *in vitro* tissue culture methods where possible.

15.83 There has been particular concern about toxicity testing of what many perceive to be trivial products, such as cosmetics and toiletry products, or medicines which are very similar to those already on the market.[47] All members of the Working Party who, in principle, can accept some forms of research involving animals, agree that unnecessary testing must be avoided. However, they were not able to agree on specific recommendations because it is not always straightforward to define a trivial use or a form of unnecessary testing. In the case of medicines, improvements are sometimes made in small increments, and although new medicines may differ only slightly from products already marketed, they may in fact be safer or more effective for particular people (see paragraphs 3.13 and 14.40). In the case of cosmetics or toiletry products there is the possibility that some people have sensitivities or allergies towards ingredients such as colorants which different manufacturers use in addition to the active ingredient. Some would therefore argue that a range of apparently identical products can be justified, since the different compositions help to take into account the variability in sensitivities among different people.

*The international context of animal research*

Problems in harmonising international test guidelines

15.84 Many tests involving animals are conducted to provide safety or efficacy data for regulatory authorities, in compliance with national or international legislation (see paragraphs 9.4 and 13.49–13.52). Thus, if various authorities require testing to be carried out using different study designs, a single chemical that is marketed in a number of countries might need to be tested several times. Harmonisation of test guidelines, so that a single study design is acceptable to regulatory authorities in many countries, is a very valuable means of reducing the use of animals in safety and efficacy testing. The ICH has managed to improve mutual acceptance for the pharmaceutical industry, but much still needs to be done to extend this approach to other product areas.

15.85 In theory, the adoption of guidelines on toxicity testing by the OECD should allow national or supranational regulatory authorities (such as the EPA (Environmental Protection Agency) or FDA (Food and Drug Administration) in the USA, or the European Commission) to incorporate them with minimal change into their own testing requirements. But in practice this has not always been the case. While, the European Commission incorporated new *in vitro* methods for skin corrosivity more than a year before their final review and approval by the OECD, the EPA made changes to the protocols for the three new *in vivo* methods for acute oral toxicity and also to a new OECD-approved *in vivo* method for predicting skin sensitisation (the mouse local lymph node assay). Thus, the EPA delayed acceptance for some time after their adoption by OECD and, in addition, the EPA's requirements for acute

46 Institute for Environment and Health (2001) *Testing requirements for proposals under the EC White Paper – Strategy for future chemicals policy* available at: http://www.le.ac.uk/ieh/webpub/webpub.html. Accessed on: 21 Apr 2005.

47 These medicines are sometimes also referred to as *me-too medicines*.

oral toxicity and skin sensitisation are no longer harmonised with those of other OECD Member States.

15.86 The lack of stringent international harmonisation poses problems. In the UK, the Home Office may only grant a project licence for safety assessment according to the use of procedures that are less severe to the animals involved than those described in a relevant OECD test guideline. This approach means that any company intending to register a product such as an agrochemical formulation in the USA is unable to conduct in the UK a substantial number of the tests required by the EPA. In addition, as most companies have policies for animal welfare that encourage the conduct of a single set of safety tests for global registration, the more severe protocols required by the EPA[48] are usually used and, in the case of UK-based companies, some or all of the testing has to be exported to other countries. There are many other examples of individual countries having different safety requirements.[49] Increased efforts must be made to standardise and harmonise testing requirements, in order to ensure that the minimum number of animals is used at the global level. **We therefore recommend that the UK through its National Coordinators at the OECD makes it a priority to identify areas in which harmonisation continues to be difficult and initiates steps to increase adoption of scientifically valid protocols that entail the least adverse welfare costs to the animals involved.** We also note that under the Inter-Departmental Concordat on data sharing, regulatory authorities aim to 'press for agreement on behalf of the UK Government for fullest provisions and procedures which enable data sharing when negotiating, updating and transposing relevant European Directives and when taking part in other international harmonisation processes'. **In order to support the proposed initiative by the National Coordinators at the OECD, we recommend that the UK Inter-Departmental Group on the Three Rs should produce or commission a report on cases where less severe protocols are not recognised internationally, whether for scientific or other reasons, and make suggestions for improving acceptance.**

15.87 International guidelines also have a crucial role with regard to welfare standards of animals involved in research. There is evidence that relevant OECD guidelines do not use important concepts such as what defines a *maximum tolerated dose, severe distress, obvious pain* or a *moribund condition* consistently (paragraph 9.35).[50] Several of the existing OECD test guidelines could also be improved with regard to issues such as environmental enrichment, and conditions of housing, as, for example, some do not specify the requirement for group housing where this would be possible.[51] All these factors can act as potential sources of avoidable suffering for the animals, and **we recommend that the OECD reviews and revises relevant guidelines to achieve greater consistency and to contribute to a wider application of the Three Rs in view of current knowledge.**

UK researchers commissioning or undertaking research abroad

15.88 There are a number of scientific, Three R-related and logistical reasons why researchers may collaborate with overseas scientists, outsource research work or obtain animals or animal-

48 For example, the use of higher dose levels in the acute oral toxicity tests and additional animals in the local lymph node assay.

49 For example, certain non-OECD countries can still demand an LD50 test, and Japan requires additional safety pharmacology tests (both *in vitro* and *in vivo*) of active ingredients for pesticides.

50 Koeter HBWM (1999) The OECD Test Guidelines Programme and animal welfare concern: how to avoid major animal suffering, in *Humane Endpoints in Animal Experiments for Biomedical Research*, Hendriksen CFM and Morton DB (Editors) (London: Royal Society of Medicine Press), pp13–14.

51 Combes RD, Gaunt I and Balls M (2004) A scientific and animal welfare assessment of the OECD health effects test guidelines for the safety testing of chemicals under the European Union REACH system *ATLA* **32**: 163–208.

derived products (such as monoclonal antibodies) from other countries. This interaction can provide a useful means of disseminating good practice developed within the UK. But there is also a need to ensure that the international nature of research is not used to introduce double standards. **We note the position statement by the Wellcome Trust, which, as a general rule, we endorse:**

> 'International research supported by the Trust is expected to be carried out in the spirit of the UK legislation as well as being compliant with all local legislation and ethical review procedures.'[52]

15.89 Further to the requirement implied in this statement, some members of the Working Party would like to see formal provisions in place which ensure that research and testing, both nationally and internationally, are always carried out in accordance with the least-severe protocols, in order to minimise harm to animals used in research. They would also welcome the introduction of regulations that would prevent UK researchers from importing or outsourcing research or research products that it would not be possible to obtain in the UK. Since the extent to which this may be occurring is uncertain, they would like to recommend that Ministers request the APC to undertake a systematic study to clarify the matter, exploring perhaps also whether a system of certification or voluntary codes of conduct would be suitable devices to ensure that UK-based researchers adhere to the same standards abroad as in the UK. From their point of view, whenever UK researchers are involved in international collaborations they should seek to adopt protocols that meet the highest international standards of best practice. As a minimum they should meet UK requirements, which in most cases are likely to be stricter than those of other countries. The group would also like to recommend that multinational companies that undertake part of their research in the UK should enforce a single global policy on animal care and welfare that meets the highest international standards of best practice.

15.90 However, other members of the group, while welcoming the aspiration behind such proposals, have reservations about their appropriateness and feasibility. They argue that because of the differences in regulatory systems it would be very complicated to ensure that research facilities abroad, or products sourced from outside of the UK met with Home Office approval. If such approval could not be attained, there would be a risk that research and testing facilities in the UK would be disadvantaged, since the exchange of products such as antisera, passaged tumours or GM lines is crucial to collaboration in fundamental research. Accordingly, they do not see a need to recommend that the APC be asked to undertake a study to advance the debate. Similarly they point out that practical problems may prevent multinational companies from implementing a single harmonised policy on animal care and welfare, both in the medium and long term.

15.91 Members also briefly discussed, but were not able to agree on, the question of whether UK-based research might be driven abroad because of the current, or likely future, regulatory provisions and practice. During our fact-finding meetings and discussions we heard conflicting evidence about this possibility. Some researchers observed that several research projects, and some laboratories, have been moved abroad while others, more frequently pharmaceutical companies, consider that the attractiveness of scientific talent in the UK generally outweighs any regulatory burdens. A range of views was represented among members of the Working Party, with some agreeing with the evidence presented during the fact-finding meetings, and others disagreeing. The latter group found arguments

52 The Wellcome Trust *Policy on the use of animals in medical and veterinary research*, available at http://www.wellcome.ac.uk/doc%5Fwtd002764.html. Accessed on: 21 Apr 2005.

against regulation unhelpful especially in view of the fact that those wishing to relax regulations often point to the strictness of the regulatory framework in order to allay concerns, for example, by members of the public. Despite these disagreements, all members of the Working Party emphasise that maintaining high standards in the UK has the potential to continue to influence regulations positively elsewhere. At the same time, the provisions of the A(SP)A and their implementation also need to be reviewed regularly in the context of national and international developments in policy and public debate.

# Appendices

# Appendix 1: Statistics - Use of animals in the UK

## Examples of the numbers of animals used for different purposes by humans

| Use | Numbers used |
|---|---|
| **Animal research (see Appendix 2)** | UK (2003): 2.79 million[1] |
| **Food**[2] | UK (2003): Total 900 million – 1 billion<br>Including: |
| Poultry | UK (2003): 871 million broiler chickens (for meat)<br>27 million hens for egg production |
| Cattle | UK (2003): 10.4 million |
| Sheep | UK (2003): 33.6 million |
| Pigs | UK (2003): 4.6 million |
| Fish | UK (2003): 631,400 tonnes[3] |
| **Working animals** | |
| Guide Dogs | UK (2004): 5,000[4] |
| Police Dogs | England and Wales (2003): 2,500[5] |
| **Clothing** | |
| Wool | UK (2002/03): 24.9 million sheep[6] |
| Fur | Fur farming is now prohibited in the UK[7] |
| **Leisure/ Education** | |
| Wildlife observation | not available |
| Companion animals/Pets | UK (1995): More than half of all households have a pet – 7.2 million cats,[8] 6.5 million dogs, 1.2 million rabbits, 135 million ornamental fish[9] |
| Zoo | UK (2003): 160 registered zoos[10] |
| Circus | UK (1997): 21 circuses with animal acts, 545 wild and exotic animals[11] |
| Hunting/shooting | UK (1999): 178 fox hunts, 3 deer hunts, 83 hare hunts and 20 mink hunts per year[12], approximately 4,000 hounds a year put down[13] |
| **Sport** | |
| Horse racing | UK (2005): 14,000 horses in training[14] |
| Greyhound racing | UK (2005): 10,000 new greyhounds registered with the National Greyhound Racing Club each year[15] |
| **Pest control** | [UK (2002): 1,300 pest-control companies – mice, rats, wasps, bees [16]] |

1 Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (Norwich: HMSO).

2 DEFRA (2003) *Statistics in Animal Health & Welfare Strategy for GB: The Evidence Base*, available at: http://www.scotland.gov.uk/library5/environment/ahwseb.pdf. Accessed on: 3 May 2005; see also RSPCA (2005) *Farm Animals*, available at: http://www.rspca.org.uk/servlet/Satellite?pagename=RSPCA/Publications/FarmAnimalsPublications&articleid=0. Accessed on: 3 May 2005.

3 DEFRA (2004) *United Kingdom Sea Fisheries Statistics* 2003, available at: http://statistics.defra.gov.uk/esg/publications/fishstat/uksfs03.pdf. Accessed on: 3 May 2005.

4 Royal National Institute of the Blind (2005) *Facts and Myths about people with sight problems*, available at: http://www.rnib.org.uk/xpedio/groups/public/documents/PublicWebsite/public_empfacts.hcsp. Accessed on: 4 May 2005.

5 BBC (2003) *Crime Fighters: Policing – Police Dog Unit*, available at: http://www.bbc.co.uk/crime/fighters/policedogunit.shtml. Accessed on: 4 May 2005.

6 The British Wool Marketing Board (2004) *Wool statistics*, available at: http://www.britishwool.org.uk/a-factsheet4.asp. Accessed on: 4 May 2005.

7 Under the Fur Farming (Prohibition) Act (2000) mink farming was banned in the UK from the beginning of 2003. British Fur Trade Association: see British Fur Trade Association (2004) available at: http://www.britishfur.co.uk. Accessed on: 3 May 2005.

8 A survey estimated that domestic cats kill 300 million wild animals annually, see The Mammal Society (1998) *Look what the cat's brought in!*, available at http://www.mammal.org.uk/catkills.htm. Accessed on: 3 May 2005; A four-year cat predation study done at the University of Wisconsin estimated that rural free-roaming cats kill at least 7.8 million and perhaps as many as 217 million birds a year in Wisconsin. See Coleman JS and SA Temple (1995) How many birds do cats kill? *Wildlife Control Technology* **44**.

9 Animal Aid, available at http://www.animalaid.org.uk/youth/topics/sport/intro.htm. Accessed on: 3 May 2005.

10 Zoos UK (2003), available at: http://www.zoos.50megs.com. Accessed on: 3 May 2005.

11 BBC News (1998) *Protect Circus animals call*, available at: http://news.bbc.co.uk/1/hi/uk_politics/201483.stm. Accessed on: 3 May 2005.

12 Burns Committee report on hunting with dogs (submitted to Secretary of State for the Home Department in 2000).

13 Burns Committee report on hunting with dogs (submitted to Secretary of State for the Home Department in 2000).

14 The Jockey Club (2005) *Key facts*, available at: http://www.thejockeyclub.co.uk/about/aboutframeset.html. Accessed on: 4 May 2005.

15 National Greyhound Racing Club (2005) *Frequently asked questions*, available at: http://www.ngrc.org.uk/default.asp?articletype=Fact%20Sheets. Accessed on: 4 May 2005.

16 Office of Fair Trading (2002) Review of undertakings given by Rentokill Initial plc: A consultation paper, available at: http://www.oft.gov.uk/NR/rdonlyres/A4D14148-39FB-42F7-8C11-AE3CE796DE85/0/oft392.pdf. Accessed on: 3 May 2005.

# Appendix 2: Statistics - Research involving animals in the UK, EU, USA and Japan

## Research involving animals

***UK – Home Office Statistics of Scientific Procedures on Living Animals, Great Britain***

The Home Office publishes detailed annual statistics on the numbers, species and purposes of all animals used in scientific procedures in Great Britain. However, for reasons related to the licensing process, the statistics focus on details about the gross number of animals used for the first time in that year, and about the number of series of procedures begun in that year. Animals used in more than one series of procedures are only counted once (see paragraph 13.27). Furthermore, as explained in Chapter 13, the statistics also do not give any information about the actual degree of pain and suffering which animals involved in procedures experience (Box 13.3).

The data summarised below relate to the statistics for 2003.[1]

- The number of scientific procedures on living animals commencing in 2003 was approximately 2.79 million.
- The total number of animals used in scientific procedures initiated in 2003 was approximately 2.72 million.

***Species of animal used in research***

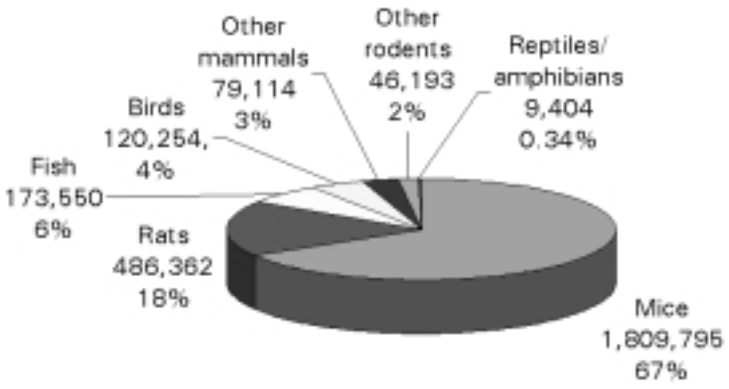


Figure 1: Species of animal used in research (numbers of animals)

| Other mammals (number of animals) | | Other rodents (number of animals) | |
|---|---|---|---|
| Sheep | 17,906 | Guinea pigs | 32,894 |
| Rabbits | 17,010 | Hamsters | 3,999 |
| Cattle | 15,822 | Gerbils | 6,509 |
| Pigs | 11,398 | Other | 2,791 |
| Dogs | 5,088 | | |
| Non-human primates | 3,073 | | |
| Cats | 547 | | |
| Other | 8,270 | | |

[1] Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (London: HMSO).

***Purposes of research***

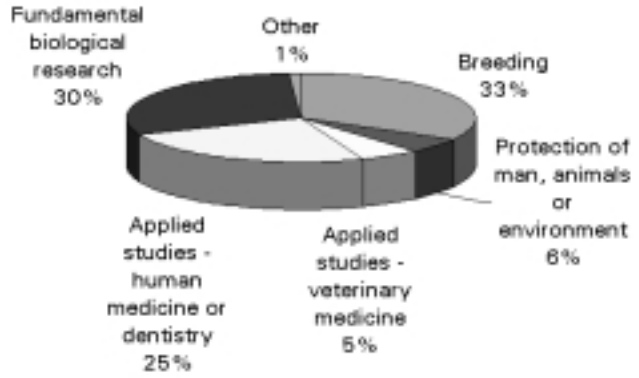


Figure 2: Primary purpose of research (% of total procedures)

The different types of research are explained in the *Statistics* as follows:

**Fundamental biological research:** research carried out with the primary intention of increasing knowledge of the structure, function and malfunction of humans and other animals, or plants. Such studies may be aimed solely at an increase in knowledge, application of that knowledge being beyond the scope of the investigation, or with a view to providing a practical solution to a medical or veterinary problem once the issues are more clearly defined and understood. This category includes physiological, pathological, pharmacological, genetic and biochemical studies, including toxicological evaluation.

**Applied studies – human medicine or dentistry, and veterinary medicine:** this category comprises research into, development of, and quality control of products or devices, including toxicological evaluation and safety or efficacy testing.

**Protection of humans, animals or the environment:** studies with the purpose of toxicological or other safety or environmental evaluation. This includes toxicological work that is not related either to fundamental research or to the solution of medical and veterinary problems. It also includes some non-toxicological procedures.

**Breeding:** a category for recording the production and breeding of animals with harmful genetic defects, and GM animals. The numbers recorded in this category include those animals which are identified as possessing a harmful mutation or are genetically modified, but are not used subsequently on procedures recorded elsewhere. The numbers recorded also include some animals which were subjected to regulated procedures such as tissue sampling or hormonal administration for the purpose of regulated breeding programmes.

Other

- *Education and training:* includes procedures carried out under project licences for the purposes of education or training under the A(SP)A. They also include killing of animals by methods not included in Schedule 1 to the A(SP)A, if the killing takes place for educational purposes at a designated establishment. Such killing may be authorised to provide, for example, tissues subsequently used for education or training. The use of animals for the acquisition of manual skills is currently permitted only for training in microvascular surgery, and at present this is always carried out under general anaesthesia, without recovery.
- *Forensic enquiries:* refers to animal use in human or veterinary enquiries relevant to potential legal proceedings.
- *Direct diagnosis:* investigation of disease including investigating suspected poisoning. Procedures may be carried out for the purpose of diagnosing disease in an individual human or

animal patient or a group of such patients. There is no research function; these are essentially applied studies, predominantly involving the production of biological reagents, for example antibodies and clotting factors.

***Toxicological procedures***

- Procedures for toxicological purposes accounted for 16% of all procedures started in 2003.
- Some of these procedures are included in the categories Fundamental biological research and Applied studies: human medicine or dentistry, and veterinary medicine. Others are included under Protection (see Figure 2).

***Severity of Procedures***

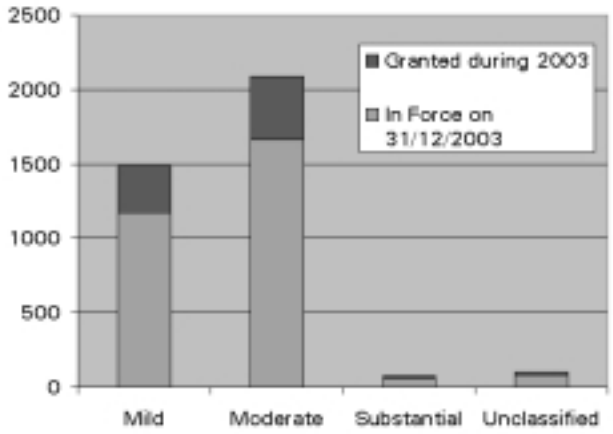


Figure 3: Number of licences by severity banding

One of four levels of severity is assigned to project licenses, based on protocols that are:

**Mild:** procedures that give rise to slight or transitory minor adverse effects, including taking infrequent blood or tissue samples from an animal, conducting skin-irritation tests with substances that are expected to be non-irritant or mildly irritant.

**Moderate:** procedures such as injecting substances to produce antibodies, toxicity tests that do not involve lethal end points, and the implantation of a microtransmitter to monitor blood pressure. In general, researchers must ensure that pain is minimised, and animals must be given pain relief. Animals that undergo surgery are given anaesthetics.

**Substantial:** procedures including major surgery, toxicity testing leading to significant morbidity or death and the use of some animals as disease models.

**Unclassified:** protocols in which animals are anaesthetised before a procedure starts and are killed without recovering consciousness.

***GM animals***

- In 2003 there were 764,000 procedures involving GM animals.
- More than a quarter of all procedures in 2003 involved GM animals.
- Ninety-seven percent of these procedures involved mice, 2% fish, 0.3% rats, 0.2% amphibians, 0.03% sheep and 0.03% domestic fowl.

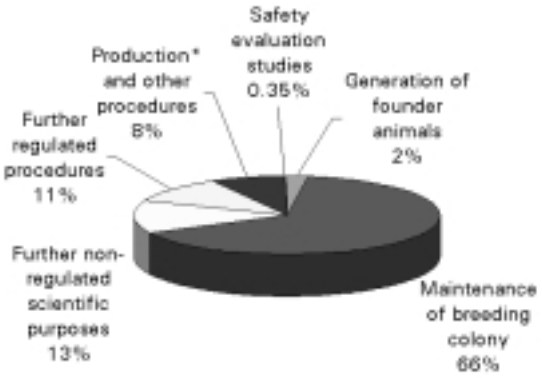


Figure 4: Use of GM animals in research by purpose of procedure (% of total procedures)

*Includes production of various biological materials such as antibodies, infections agents, plasma and tissues.

## International

***Europe***

Under European Council Directive 86/609/EEC on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes, EU Member States are 'required to collect, and as far as possible periodically make publicly available, the statistical information on the use of animals in experiments'.

The European Commission has produced four reports for the Council and the European Parliament on the number of animals used for experimental and other scientific purposes in Member States of the EU. The reports are published approximately every five years and the last report was published in 2005 concerning data from 2002.

The data summarised below relates to the statistics of 2002.[2]

- The total number of animals used for experiments in the EU was 10.7 million.
- Rodents and rabbits amounted to 78 percent of the total animals used in the EU; 15 percent of animals used were fish and other cold-blooded animals. The proportion of primates was 0.1% of all animals used.
- Animals used for toxicological and other safety evaluation represented 10% of the total number of animals used for experimental purposes.

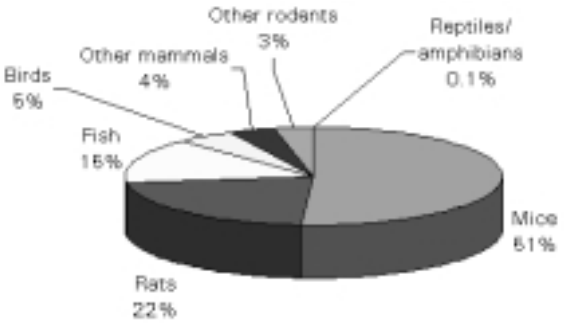


Figure 5: Animals used in research in the EU in 2002 by species (numbers of animals)

[2] Statistics for 14 member states concerning 2002. Please note that France submitted statistics for 2001. European Commission (2005) *Fourth Report from the Commission to the Council and the European Parliament on the Statistics on the number of animals used for experimental and other scientific purposes in the member states of the European Union*, available at: http://europa.eu.int/comm/environment/chemicals/lab_animals/pdf/com_2005_7_en.pdf. Accessed on 5 Apr 2005.

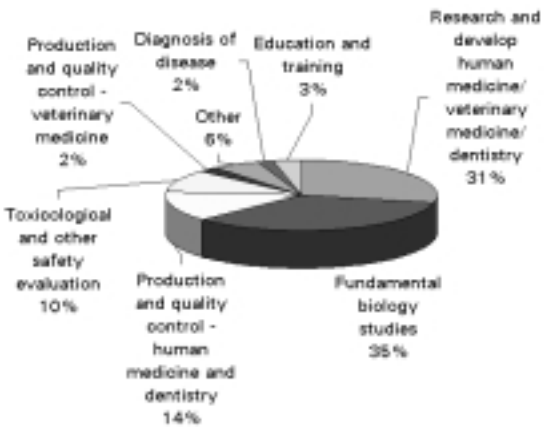


Figure 6: Research using animals conducted in the EU in 2002 by study type (% of total number of animals)

***USA***

Three bodies oversee the welfare of research animals in the USA: the US Department of Agriculture (USDA), the Department of Health and Human Services (DHHS) and the Association for the Assessment and Accreditation of Laboratory Animal Care (AAALAC).

The USDA has in the past produced an annual report on the enforcement of the Animal Welfare Act. This includes statistics on the number of animals used in research. The most recent report was published in 2003 for the fiscal year of 2002. As this report relates specifically to the US Animal Welfare Act, birds, rats and mice bred for use in research are excluded.[3]

The data summarised below relate to the statistics of the fiscal year of 2002 (October 2001–September 2002).[4]

- Approximately 1.1 million animals were used for research in US federal and industrial research laboratories.

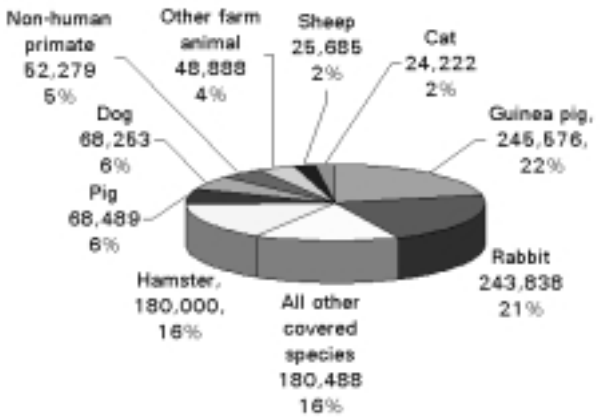


Figure 7: Animals used for research in the USA October 2001–September 2002 by species (excluding birds, rats and mice;[5] total numbers of animals)

[3] Birds, rats of the genus Rattus and mice of the genus *Mus*, bred for use in research are not included in the term 'animal' under the Animal Welfare Act. This is based on practical difficulties, rather than philosophical objections. Federal Register (2004) Rules and Regulations Vol. 69, No. 108 4 Jun; House of Lords Select Committee on Animals in Scientific Procedures (2002) *Volume 1 – Report* (London: TSO).

[4] USDA (2003) *Annual Report of Enforcement for the Fiscal Year 2002* (Riverdale, MD: USDA), available at: http://www.aphis.usda.gov/ac/2002ar/ar2002.pdf. Accessed on: 13 Jan 2005.

[5] Federal Register (2004) Rules and Regulations Vol. 69, No. 108 4 Jun; House of Lords Select Committee on Animals in Scientific Procedures (2002) *Volume 1 – Report* (London: TSO).

***Japan***

There are no official statistics for the use of animals in scientific procedures in Japan. A voluntary survey is conducted every four or five years by the Japanese Association for Laboratory Animal Science (JALAS):

- The most recent survey covered April 2001–March 2002 for which 889 researchers of universities, institutes, testing laboratories and companies were polled (response rate 57%).
- These figures total approximately 4.7 million animals.
- Almost 2 million of these were GM animals, 99% of which were mice.

The data summarised below relate to the period between April 2001 and March 2002.[6]

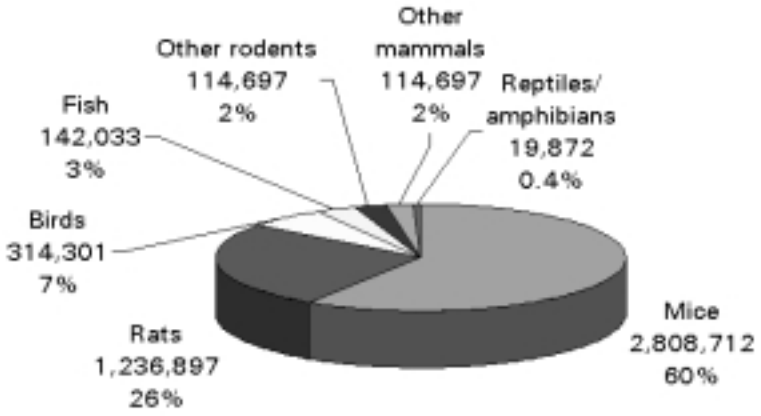


Figure 8: Animals used in scientific procedures in Japan April 2001–March 2002 by species (numbers of animals)

- A separate survey conducted by the Japanese Association for Laboratory Animals in National Universities (JALAN) estimated that approximately 1.28 million animals were used in experiments by medical education and research institutes in 1999.[7]

6 Committee for Laboratory Animal Care and Use (2003) The number of live animals used in experiments in 2001 – results of a survey *Exp Anim* **52**: 143.

7 Ninomiya H and Inomata T (1998) Current uses of laboratory animals in Japan and alternative methods in research, testing and education *App Anim Behav Sci* **59**: 219–25; Matsuda Y (2004) Recent trends in the number of laboratory animals used in Japan *ATLA* **32**, Supplement 1: 299–301.

# Appendix 3: Reports by other organisations


- Agriculture and Environment Biotechnology Commission (2002) *Animals and Biotechnology* (London: DTI)
- Animal Aid (2003) *Monkeying Around with Human Health: The cost to people of experiments on primates* (Tonbridge: Animal Aid)
- Animal Procedures Committee (2001) *Biotechnology* (London: APC)
- Animal Procedures Committee (2003) *Consultation paper on the statistics of scientific procedures on living animals in Great Britain* (London: APC)
- Animal Procedures Committee (2001) *Openness* (London: APC)
- Animal Procedures Committee (2003) *The use of primates under the Animals (Scientific Procedures) Act (1986)* (London: APC)
- Animal Procedures Committee (2003) *Review of cost-benefit assessment in the use of animals in research* (London: HO)
- The Associate Parliamentary Group for Animal Welfare (2005) The use of animals in vaccine testing for humans (London: APGAW)
- Biotechnology and Biological Sciences Research Council (2003) *Science and Animal Welfare* (Swindon: BBSRC)
- Boyd Group (1999) *Genetic Engineering: Animal welfare and ethics* (Southsea: Boyd Group)
- Boyd Group (2002) *The Use of Non-human Primates in Research and Testing* (Southsea: Boyd Group)
- Boyd Group (2002) *The Use of Animals in Household Products* (Southsea: Boyd Group)
- British Union for the Abolition of Vivisection (2002) *An investigation by the BUAV into primate research at Cambridge University* (London: BUAV)
- British Union for the Abolition of Vivisection (2003) *Designer Mice* (London: BUAV)
- British Union for the Abolition of Vivisection/European Centre for the Validation of Alternative Methods (2001) *The Way Forward: A non-animals testing strategy for chemicals* (London: BUAV)
- European Centre for the Validation of Alternative Methods (1998) *The Use of Transgenic Animals in the European Union: The Report and Recommendations of ECVAM Workshop 28* (Ispra: ECVAM)
- European Group on Ethics in Science and New Technologies (1996) *Opinion on the Ethical Aspects of Genetic Modification of Animals* (Brussels: EC)
- European Science Foundation Policy Briefing (Second Edition) (2001) *The Use of Animals in Research* (Strasbourg: ESF)
- Genewatch UK (2002) *Genetically Modified and Cloned Animals: All in a good cause?* (Buxton: Genewatch)
- House of Lords Select Committee (2002) *Animals in Scientific Procedures* (Norwich: TSO)
- Medical Research Council (2004) *Ethics Guide: Best practice in the accommodation and care of primates used in Scientific Procedures* (London: MRC)

- Medical Research Council (2000) *Mice and Medicine: Animal experiments, medical advances and the MRC* (London: MRC)
- Royal Society (2001) *The Use of Genetically Modified Animals* (London: Royal Society)
- Royal Society (2004) *The Use of Non-human Animals in Research: A guide for scientists* (London: Royal Society)
- Royal Society for the Prevention of Cruelty to Animals (2001) *Counting the cost – primate transport* (Horsham: RSPCA)
- Royal Society for the Prevention of Cruelty to Animals (2000) *Safe and sound – the use of animals in cosmetics testing* (Horsham: RSPCA)
- Royal Society for the Prevention of Cruelty to Animals (Smith JA and Jennings M) (2003) *A Resource Book for Lay Members of Local Ethical Review Processes* (Horsham: RSPCA)
- Straughan R (1999) *Ethics, morality and animal biotechnology* (Swindon: BBSRC)

# Appendix 4: Method of working

In 2001, the Council held a workshop that addressed ethical issues arising from research involving animals. Subsequently, in February 2003, the Working Party on the ethics of research involving animals was established. Twelve meetings were held between February 2003 and December 2004.

As part of its work, the Working Party held nine fact-finding meetings. Five of these took the form of discussions with experts and stakeholders at the offices of the Nuffield Council. Four meetings took place at animal research facilities, where members familiarised themselves with the practice of research, and discussed scientific, ethical and legal issues with those involved. Brief descriptions of these meetings are provided below.[1]

The Working Party also commissioned three evidence reviews relating to the assessment of pain, suffering and distress in animals. These were provided by Professor Colin Allan, Professor Marc Bekoff and Professor David Morton.

From September to December 2003, the Working Party held a wider consultation, the responses to which are summarised in Appendix 5.

The Working Party is extremely grateful to all those who took the time and contributed to its work by providing valuable insights and helping to clarify the complexities of scientific, regulatory, social and ethical issues raised by research involving animals.

## Fact-finding meetings[2]

***14 May 2003, London***

Meeting at 28 Bedford Square, as part of the second meeting of the Working Party

*Michele Corrado*
Director of Social and Health Research, MORI Social Research Institute

Programme:

- Presentation of a recent study by MORI for CMP (Coalition for Medical Progress) on attitudes of members of the public towards research involving animals;
- discussion about the findings of the research and methodological issues concerning the generation, presentation and use of data arising from polls.

***2 July 2003, Pfizer, Sandwich***

Members of the Working Party who attended the meeting included Baroness Perry of Southwark (Chair), Professor Barry Keverne FRS, Professor Martin Raff FRS, Nick Ross, Professor Jonathan Wolff, Dr Sandy Thomas and Harald Schmidt

Staff at Pfizer:

*Dr Gill Samuels CBE*
Senior Director, Science Policy and Scientific Affairs

[1] The Working Party also intended to familiarise themselves with the practice and rationale of primate research classified as 'substantial'. This interest was discussed with staff of the Home Office and it was agreed that the Home Office would forward a letter outlining the Working Party's request to visit research facilities that undertook such research. A letter was sent to the Home Office in February 2004. The Council received one reply from a research institute in July 2004, and contact was initiated to schedule a visit. However, it did not prove possible to arrange a fact finding meeting. Staff at the research institute were concerned about the institutional affiliations of some members of the Working Party.

[2] Institutional affiliations at the time of the meeting are listed.

*Graham Moore*
Consultant (Science Policy and Scientific Affairs)

*Anon.*
Certificate Holder

*Anon.*
Named Veterinary Surgeon

*Anon.*
Named Animal Care and Welfare Officer

*Anon.*
Director of Animal Welfare

*Anon.*
Project Licence Holder – Veterinary Medicines

*Anon.*
Personal Licensee – Human Medicinals

*Anon.*
Home Office Liaison Officer

Programme:

- Introduction to drug discovery and development at Pfizer;
- discussion: sourcing, husbandry and use of animals in human and veterinary research, transferring results from animals to humans, regulatory aspects of animal research, ethical review and decision making, engagement with the public and information programmes;
- tour of the 'small animal' animal facilities and discussion with staff on current medicines research programmes involving rodents and terminally anaesthetised rabbits (a scheduled visit to the dog laboratories was cancelled because the facilities were not accessible on the day of the visit due to construction work; however, members were invited to view these on another occasion);
- tour of non-animal research area and introduction to Automated Laboratory In Vitro Assay Systems (ALIAS).

***16 September 2003, London***

Meeting at 28 Bedford Square, as part of the fourth meeting of the Working Party

*Rosie Barnes*
Chief Executive, Cystic Fibrosis Trust

*Christine Cryne*
Executive Director, Muscular Dystrophy Campaign

*Robert Meadowcroft*
Director of Information, Policy and Research, Parkinson's Disease Society

Programme:

- Introductions to the campaigning and information activities of the charities;
- discussion about the usefulness of animal models for cystic fibrosis, muscular dystrophy and Parkinson's disease; decisions about funding research on animals; outreach and relation to activist groups; concerns of members of charities about research on animals and the question of whether or not it poses a moral dilemma.

***3 October 2003, Biology Department, University of York***

Members of the Working Party who attended the meeting included Nick Ross, Professor John Spencer, Professor Jonathan Wolff, Dr Sandy Thomas and Harald Schmidt.

Staff at the Biology Department of the University of York:

*Dr Patricia Coulson*

*Dr Betsy Pownall*

*Dr Harv Isaacs*

*Professor Henry Leese*

*Professor Alan Wilson*

*Mike Snelling*

*Professor Alistair Fitter*

*Dr Piran White*

*Professor Geoff Hall*

Programme

- Introduction to basic and applied research involving amphibians and rodents;
- tour of the animal facilities and discussion of scientific, regulatory and ethical issues with staff and students relating to developmental studies on fertilised eggs of frogs; studies for improved fertility treatment using mice, and cattle and pig embryos; the development of a *schistosomiasis* vaccine involving snails, worms and mice.

***3 October 2003, the contract research organisation Covance (a contract research organisation), Harrogate***

Members of the Working Party who attended the meeting included Nick Ross, Professor John Spencer, Professor Jonathan Wolff, Dr Sandy Thomas and Harald Schmidt

Staff at Covance:

*Dr Chris Springall*
Vice President, Toxicology

*Colleagues with expertise in toxicology research and ethical review*

Programme:

- Introduction to scientific and regulatory aspects relating to the toxicity testing of new medicines and agrochemicals;
- tour of the animal facilities and discussion of scientific and animal welfare related issues with staff concerning research on pregnant rabbits to assess the toxicity of a pesticide on fetuses; the testing of anti-diabetes compounds in mice; research involving captive-bred macaque monkeys; and systemic toxicity studies in beagles;
- discussion of methodological and regulatory issues relating to toxicity testing including the function and adequacy of the severity banding of the Home Office and the scientific scope and limitations of alternatives to tests such as the Draize test.

***4 November 2003, London***

Meeting at 28 Bedford Square, as part of the fifth meeting of the Working Party

*Professor Michael Balls*
Trustee, FRAME, former Head of the European Centre for the Validation of Alternative Methods (ECVAM)

*Dr Gill Langley*
Scientific Advisor, Dr Hadwen Trust for Humane Research

Programme

- Introduction to the activities of ECVAM and the Dr Hadwen Trust with regard to the promotion of the acceptance of alternatives to animal research;
- discussion of recent qualitative and quantitative trends in the use of animals in research; the relation of replacement to refinement and reduction strategies; the nature of barriers to the uptake of replacement alternatives; the possible focus of the newly established National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs); the role of the Three Rs in the regulatory framework of the UK; the potential of the Three Rs in different areas of basic and applied research.

***8 January 2004, London***

Meeting at 28 Bedford Square, as part of the sixth meeting of the Working Party

*Dr Jon Richmond*
Head, Animals (Scientific Procedures) Division (ASPD), Home Office

*Professor Michael Banner*
Chair, Animals Procedure Committee (APC)

*Richard West*
Secretary, Animals Procedure Committee (APC)

Programme:

- Introductions to the role and functioning of the ASPD and the APC;
- discussion of specific issues relating to the application of the A(SP)A: the inspection system; the operation of the cost-benefit analysis; the relationship of UK regulation to international regulations, the role of the APC in offering advice to the Home Office about a small number of applications for research, mostly involving the use of non-human primates in the 'substantial' category of severity; the nature and relevance of the severity banding system; the presentation of data in the statistics published by the Home Office; obstacles to a wider implementation of the Three Rs.

***11 March 2004, London***

Meeting at 28 Bedford Square, as part of the seventh meeting of the Working Party

*Dr Ray Greek*
President, Americans For Medical Advancement (AFMA); Medical Director, Europeans For Medical Advancement (EFMA)

*Kathy Archibald*
Director, EFMA

Programme

- Introduction to the activities of AFMA an EFMA;
- Discussion on scope and limitations of transferability and predictability of data obtained from animals for the study of human diseases, including cancer, HIV/AIDS, polio, TSE and others; the question of whether or not animal testing was in fact more dangerous than beneficial for humans; the role of animal research questions relating to the liability of pharmaceutical companies; the potential of alternatives to animal research.

***21 March 2004, Institute of Neurology, London***

Members of the Working Party who attended the meeting included[3] Baroness Perry of Southwark (Chair), Dr Maggy Jennings, Dr Mark Matfield, Professor Jonathan Wolff, Dr Sandy Thomas and Harald Schmidt.

Staff at the Institute of Neurology:

*Professor Roger Lemon BSc PhD MA FMedSci*
Director, Institute of Neurology (Project Licence Holder)

*Robert Walker*
Institute Secretary and Home Office Certificate Holder

*Martin Lawton*
Named Veterinary Surgeon

*John Frogley*
Superintendent, animal house facilities

Programme

- Introduction to the Institute of Neurology's research programme in the areas of epilepsy, multiple sclerosis, spinal cord injury, Parkinson's disease, headache and migraine;
- discussion of examples of research areas in which the use of non-human primates was indispensable: deep-brain stimulation (DBS) for the treatment of Parkinson's disease, and research to understand the use of transcranial magnetic stimulation (TMS) for diagnosis and treatment of movement disorders, spinal injury and depression;
- viewing of a video illustrating current research on the effects of stroke on the function of the human hand. Research involved the recording of neural activity in captive-bred, awake macaque monkeys. Two members of the Working Party viewed an experiment in progress;
- discussion of scientific, methodological, animal-welfare-related and ethical issues arising from primate research: transferability and predictability; breeding, housing and handling of primates; interactions with the Home Office; future scientific uses of non-human primates; the role of undercover investigations of animal-rights activists.

[3] We regret that it was not possible for all members of the Working Party who wished to attend this fact-finding meeting to do so. The Institute of Neurology took the decision not to invite Michelle Thew as they understood that she had been associated, through her previous professional affiliation with the British Union for the Abolition of Vivisection (BUAV), with undercover investigations and intimidation of staff similar to that at the Institute of Neurology. The Institute commented that 'It is not acceptable for this Institute or its staff to engage in an open dialogue with those who have chosen infiltration, and whose organisations have openly threatened individual scientists who work here.' Michelle Thew stated that neither she, nor the BUAV as an organisation, had been involved in any undercover investigation at the Institute, nor had she or the BUAV threatened staff of the Institute in any way. Professor Lemon acknowledged at a later stage that the infiltration at the Institute of Neurology had in fact been organised by the National Anti-Vivisection Society (NAVS).

***14 January 2005, Huntingdon Research Centre (HRC), Huntingdon; Huntingdon Life Sciences (HLS), Huntingdon***

Members of the Working Party who attended the meeting included Baroness Perry of Southwark (Chair), Professor Martin Raff, Dr Sandy Thomas and Harald Schmidt

Staff at HLS:

*Mr Brian Cass*
Managing Director HLS

*Mr Andrew Gay*
Marketing and Communications Director

*Mr David Whittaker*
Director, Laboratory Animals Sciences, Certificate Holder

Programme:

- Introduction to structural organisation and HLS business profile as a contract research organisation that undertakes developmental research on pharmaceutical, agrochemical, nutraceutical, veterinary and industrial chemicals. Discussion about functioning of the Ethical Review Process and scientific and regulatory aspects of toxicity testing;
- visit to the animal facilities and discussion with animal technicians and other staff. Viewing of part of a chronic toxicity, snout-only exposure study involving beagles. Visit to the dog and mini-pig holding facilities;
- discussion about the forms and implications of organised unlawful protests against the company.

# Appendix 5: Consultation with the public

A Consultation with the public was held between October and December 2003. Nearly 600 copies of the Consultation paper were disseminated and a further 2,503 were downloaded from the Council's website. There was also the opportunity to comment online on the questions posed. One hundred and sixty-eight responses were received from both individuals and organisations. The Council welcomed the many and varied responses from nine different countries. A summary of the responses to six specific questions asked in the Consultation document is set out below. A list of respondents follows the summary. Many respondents agreed to make their full submissions available to the wider public and their comments can be found on the Council's website.[1]

The Working Party would like to thank everyone who contributed to the Consultation.

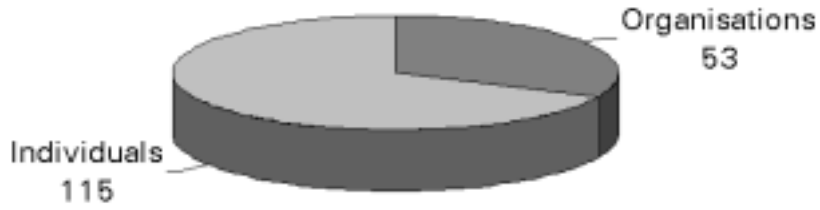


Figure 1: Breakdown of response – individuals and organisations

## What is your view about the use of animals in research?

Many respondents stated that, in their view, research involving animals had led to considerable advances in biology and medicine. They said that it would not be possible to exclude animal use without compromising safety or slowing progress, as research involving animals provided information which was not otherwise obtainable.

Of the respondents who supported research, a significant number did not favour the indiscriminate use of animals for human purposes. Rather, they felt that the acceptability of experimental work on animals depended on the purpose of the research, the amount of suffering and the species involved. Some respondents felt that there were defined areas which should be excluded such as the testing of cosmetics and household chemicals (the former is not permitted in the UK). Some people accepted animal experimentation which involved mild or moderate procedures on certain species, but found substantial procedures unacceptable. Several respondents described the creation of animals with reduced sentiency or which would endure continuous suffering as deplorable.

Scientists and scientific organisations submitted responses stating that basic research was crucial. They observed that this type of research may seem more difficult to justify, as by definition it did not promise immediate or obvious application. However, they argued that, it was responsible for major developments in biological and medical understanding.

There were also many respondents who wrote to express their dissatisfaction with research involving animals. The majority of these respondents took the view that using animals was unethical and should not be practised, regardless of the purpose. Others believed that results

[1] See http://www.nuffieldbioethics.org/go/ourwork/animalresearch/introduction.

obtained from animals were not transferable to humans and could be misleading and dangerous. They asserted that using animal models has slowed medical progress.

Many of those who expressed their view that research involving animals was unethical were concerned about the level of suffering experienced by laboratory animals. One respondent noted that pain was not always minimised, for example during pain research. A number of respondents were specifically concerned about husbandry and housing conditions and thought that these could be improved.

A few respondents questioned medical research *per se*, commenting that many modern human ailments were caused by unhealthy lifestyles and that these could be overcome without recourse to research on animals.

### What are your views about the use of GM animals in research?

Generally, those who accepted research involving animals seemed to consider that genetically modified animals have proved useful research 'tools' and have allowed researchers to generate useful models of human diseases. Certain scientific advantages of GM animals were highlighted, for example, genetic changes could be made in a short timespan and research could be carried out which would not be possible in humans. Advances in this field seemed to be especially welcomed if they have resulted in the replacement of primates or other large animals with rodents. Some scientists who work with genetically modified animals reported that, in their view, the vast majority of modifications had no obvious harmful features in the animal.

Some of those who accepted the technology thought that it was given undue focus, and that the issue of welfare should be the more important consideration. They generally agreed with opponents to genetic modification that welfare implications could not easily be predicted, which may lead to suffering. Certain groups proposed increasing the availability of information regarding phenotypes and optimal husbandry conditions for these animals. It was felt that the sharing of knowledge could reduce the replication of experiments by different groups of researchers.

Many other respondents were opposed to the genetic modification of animals on the grounds that they felt it was unnatural and breached the intrinsic value of an animal. There were concerns that the result would be the increasing commodification of animals for human purposes. Others questioned the validity of the concept of genetic engineering in pathology, arguing that, as many diseases were multifactorial and affected by the environment, it was misleading to try to understand them by changing one or two genes.

A core concern was the 'wastage' of animals in genetic modification processes. In contrast, one response gave examples of best practice which would minimise the number of surplus animals. For example, embryos could be frozen and stored for later use rather than maintaining breeding colonies which were not actually going to be used in any procedures. Respondents noted the potential increases in animal morbidity and mortality that may accompany developments in genetic modification technologies.

Cloning raised new issues for some respondents. They commented on the low success rates and high occurrence of adverse effects seen in cloned animals. Others were anxious about causing irreversible changes in biodiversity, for example if genetically altered animals were to escape into the environment. With regard to xenotransplantation it was thought by some that new viruses might emerge.

## What is your view about the use of alternatives?

The majority of respondents who commented on this subject were in favour of increasing research into alternative methods. Views ranged from those who felt that practically all results currently obtained using animals were achievable by other means, to those who would like to see further use of alternatives to supplement animal research. It was proposed that research into alternatives should not focus on replacing each conventional procedure with one that does not involve animals; Instead entire alternative approaches could be investigated.

The view that research into alternatives could be better funded was widely expressed. There were a variety of suggestions as to potential sources of funding, including pharmaceutical companies, corporate taxes, taxpayers, research councils, charities and abolitionist groups. It was important to some respondents that a lack of funding might mean that researchers were currently unable to distinguish if alternatives were possible in principle. There was support for the establishment of a National Centre for the Three Rs, which would be dedicated to the development of alternatives in addition to the refinement of experimental procedures. Others felt that research on the Three Rs should be encompassed within mainstream science rather than separated from it. This was based on the view that specific earmarking of support for alternatives could be wasteful, and therefore these funds would be better spent on further research. Contrary to this opinion was the view from one respondent that concern about the Three Rs was a smokescreen to deflect attention from the fact that animal research was scientifically flawed. For example, some stated their belief that if research involving animals were completely prohibited, research into alternatives would result in a huge leap in capabilities as 'necessity is the mother of invention'.

Several people would prefer to see more extensive use of human volunteers than was currently the case. They were anxious that future legislation would further reduce the research carried out on humans and human tissue and would therefore lead to increased animal use.

Scientists wrote to assert that, wherever possible, they already used alternative methods rather than animals and that peer review and review by funding bodies and the Home Office ensured that this was the case. They noted that animal research was expensive and inconvenient. They argued that alternatives did not always provide a similar level of complex information as experiments using animals. According to some of these respondents, alternatives offered simplified systems which could result in simplified and misleading data.

Those who held the opposing view contended that approaches using alternatives were not taken seriously by scientists and regulatory bodies. It was suggested that the latter, for example, could take a more positive view of alternative testing in toxicology studies. It was predicted that this would require more funding for validation.

Several respondents felt that it was important that scientists increase the extent to which they share their research results, including 'negative' results (i.e. results from research that was regarded as unsuccessful and which was not subsequently published). It was felt that greater sharing would reduce duplication and therefore animal use. However, it was also argued that it was improbable that two pharmaceutical companies, for example, would be working on exactly the same chemical entity and that a certain amount of replication was therefore an essential component of research. It was also suggested that published research papers could include more in-depth discussion of the methodologies used, including advice to other researchers regarding humane endpoints and potential welfare implications of research.

## What is your view about ethical issues relating to the use of animals in research?

Many people responded to the Consultation with their view that the use of animals in research was unethical in principle. They observed that if animals were so like humans that results from

animal experiments were valid for humans, then these similarities made it unethical to use animals for experimentation. They felt that all living creatures should be given the same level of compassion because they believed animals and humans had the same moral status. A number of people compared the use of animals to the use of humans by other humans, such as abuses carried out by Nazis preceding and during the Second World War.

Some of the respondents felt that research involving animals was unethical because of their belief that the concept was scientifically flawed and actually caused a slowing of medical progress. A different argument was presented by others who felt that humans had a responsibility or duty of care and compassion for other species. Several of these respondents drew comparisons between research and the use of animals for food, pets, clothing and sport, which they also thought unacceptable and unethical. Some people considered that those who denied that animals suffer should be considered as dangerous because their arguments could be used to deny that other groups of humans suffer.

For many people who responded to the Consultation, welfare and the prevention of suffering were paramount, independent of the question of whether the animals possessed 'higher' mental states or cognitive capacities. However, others thought that self-awareness and cognitive ability were more significant, because suffering could be connected to being able to recollect events of the past and anticipate the future. Some were concerned that researchers did not recognise symptoms of pain, or that observation of animal behaviour was not a reliable means of assessing suffering. These respondents believed that, based on their personal experience, many species were capable of complex thoughts and emotions. There was consensus that there should be increased research into welfare, suffering and awareness.

Contrary to these viewpoints, many other respondents considered that there was a moral duty to undertake research to alleviate human suffering and to improve quality of life. They accepted that if research involved animals, then it was ethical to use them for this purpose. In the view of many respondents, the acceptability of a particular type of research depended on the purpose. For others it was the level of suffering that constituted the overriding factor in deciding whether research should or should not be carried out. The majority of these commentators also drew distinctions between the use of different species, noting that most people practise some 'speciesism' in their daily lives.

Some people favourably compared animal research to animals used for other purposes or even those living in the wild. It was felt that ethical considerations should be consistent. One respondent believed that it was important not to be too anthropomorphic about what we conceive as quality of life for other animals. Others felt that animals did not have the capacity to act rationally as moral agents and could therefore not have 'rights'.

## What is your view about the UK regulations on research involving animals in the UK?

The regulations which govern animal research were clearly important to the majority of respondents. Views on the current UK regulations were divided, with many arguments being expressed. Views ranged from those who considered that regulations were overly prescriptive to those who thought that they were insufficiently strict and therefore ineffective. Within this spectrum were others who believed the regulations to be appropriate as they stand. It was widely held that the UK regulations were stricter than those in other countries.

Some thought that the nature of the care procedures at individual establishments were more important than the role of the Home Office Inspectorate. One respondent wished to point out that violations of the regulations have rarely led to prosecutions for staff in research establishments. There was the suggestion that licence applications should be assessed by an independent panel, not

composed of members of the government or civil service. The Inspectorate, which consisted of 25 inspectors in 2003, was felt by some to be insufficiently staffed. It was suggested that if the number of inspectors were increased, then more unannounced visits to research establishments could take place.

Some respondents considered that simplification and flexibility of project licences would be beneficial for animal welfare. These respondents, often involved in animal research, believed the regulations to be strict and thorough and sometimes overly bureaucratic. They felt that any further tightening of the legislation would stifle research, slow down progress, increase costs and could drive researchers away from the UK.

The development of the Ethical Review Process in the previous six years was highlighted. One respondent felt that the lay member on ethical review panels had limited involvement, although others felt that lay members frequently made valuable contributions. Some noted that the Animal Procedures Committee had made recommendations regarding improvements to regulation; and suggested that these be implemented.[2]

Some respondents considered the concept of the cost-benefit assessment to be flawed because costs to animals were not given due weight. The regulations state that research involving animals should only be undertaken in the absence of alternatives. However, some people alleged that this limitation could not be adhered to until further research into alternatives was conducted, as alternatives may be possible but have simply not been developed. The regulations also rely on assessments made in advance of experimentation; many respondents questioned how researchers could make welfare assessments in advance and felt that evaluations should be made before, during and after procedures are applied.

A core concern was how the regulations related to genetically modified (GM) animals. Some took the view that they were inadequate and had been written before the advent of new technologies which have resulted in the creation of GM animals. It was pointed out that current Home Office statistics included GM animals kept to maintain breeding colonies. This meant that the statistics misrepresent the proportion of rodents as compared with other animals used in actual scientific procedures. Others felt the status quo should prevail, and licences should be required for all GM breeding.

The Home Office system of classification for procedures was criticised by some respondents who questioned the use of the term 'moderate' for certain research carried out on primates. They argued that a 'substantial' procedure could be hidden within a 'moderate' project. In addition, some people objected to the fact that the terminal sedation of an animal could be termed 'unclassified'.

It was suggested that greater effort could be made to harmonise regulations regarding animal research in different countries, at least across the EU. A number of respondents considered that there was insufficient protection for people and institutions involved in animal research and would like to see regulation introduced to overcome this. There were particular concerns about violent extremists.

## What do you think about the information that is available to the public about research involving animals?

The majority of people who commented on this question felt that more information on the use of animals in research would be welcome. Some suggested that anonymised licence applications should be published and one professional body agreed, stating that the non-confidential parts of licences should be available to the public. Alternatively, or in addition, lay summaries could prove

[2] Animal Procedures Committee (2003) *Review of the cost-benefit assessment in the use of animals in research* (London: HO).

useful for interested members of the public. In contrast to this view, some scientists took the view that simplification would distort the nature and context of animal research.

It was noted by some respondents that results of animal research were published in the scientific literature and therefore available, but concerns were expressed regarding the perceived insufficient information regarding the actual use of the animals, husbandry and the role of the Three Rs. The scientific and medical language used in such publications was also recognised as a barrier to public understanding.

It was accepted that animal rights groups have provided much information to the public regarding research involving animals. Supporters of these groups considered that they had performed a valuable public service in exposing cruelty and bad practice. However, others took the view that the information that they provided was inaccurate, alarmist or out of date.

Charities fund a significant proportion of medical research involving animals and certain respondents remarked that they seemed reluctant to acknowledge the part that they played in the projects that they fund. They felt that charities should be more open. Others felt that it was difficult to persuade researchers to speak about their work in public, as they then become a target of extremists. Other suggestions for provision of information included education in schools and making available leaflets regarding animal research in doctors' surgeries and hospital waiting areas.

On the question of who could be trusted in order to obtain reliable information regarding research involving animals, it was felt by some that the current official sources of information were biased towards those who carried out such research and tended to present only the positive side of the work. These respondents felt that it was therefore difficult to trust companies which made a profit from research involving animals. Conversely, other respondents felt that they would not trust any organisation which promotes unlawful direct action against researchers or institutions. Rather, there was a call for an independent body which would balance the different interests of both stakeholders and the general public.

It was suggested by a number of respondents that they would like to 'see inside' animal laboratories; perhaps through the use of CCTV camera. Others considered that a wealth of information regarding animal research already existed, which is available to anyone who is interested, especially via the Internet.

The Council asked a secondary question in its Consultation paper regarding whether medicines that have been developed using animals should be labelled as such. Many people supported this idea. There was concern by one respondent that such labelling would lead to an increase in the number of people who refuse medication tested in this way, and who therefore demand resources to provide alternatives. There was a concern that pharmaceutical companies might try to mislead the public they would use on such labels.

## Responses to the Consultation with the public

The Working Party wishes to thank the following individuals and organisations for their interesting and helpful responses (the sign [*] indicates that permission has been granted to make the response available on the Nuffield Council's website):[3]

***Organisations***

Anonymous (1)

Animal Aid, UK (Andrew Tyler, Director)*

Animal Health Trust, UK

Association of Medical Research Charities (AMRC), UK*

Association of the British Pharmaceutical Industry (ABPI)*

AstraZeneca Pharmaceuticals, UK*

Bayer HealthCare, International

BioIndustry Association (BIA), UK

Biosciences Federation, UK*

Biotechnology and Biological Sciences Research Council (BBSRC), UK*

Professor David R Katz, on behalf of Board of Deputies of British Jews*

Boyd Group, UK*

British Psychological Society Research Board's Standing Advisory Committee on the Welfare of Animals in Psychology*

British Society of Animal Science (BSAS)*

British Union for the Abolition of Vivisection*

British Veterinary Association

Bromley Local Research Ethics Committee (NHS), UK*

Canadians for Health Research*

Committee for Ethical Issues in Medicine, Royal College of Physicians of London, UK*

COST (European Co-operation in the field of Scientific and Technical Research) Technical Committee on Medicine and Health, Brussels*

Covance Laboratories and the British Toxicology Society, UK*

The Dr Hadwen Trust for Humane Research, UK*

European Federation of Pharmaceutical Industries and Associations (EFPIA), Brussels*

Europeans for Medical Advancement, UK*

Genetic Interest Group, UK*

GeneWatch, UK*

Hellenic National Bioethics Commission, Greece*

Henderson Global Investors: Sustainable and Responsible Investment Team, UK*

Humane Research Trust, UK*

Humane Slaughter Association, UK*

Humane Society of the United States: Animal Research Issues Section*

Imperial College London Central Ethical Review Process Committee, UK

Institute for Animal Health, Compton Laboratory, UK

The Institute of Animal Technology, UK*

International Primate Protection League UK*

[3] See http://www.nuffieldbioethics.org/go/ourwork/animalresearch/introduction.

Laboratory Animal Science Association (LASA), UK*
Laboratory Animals Veterinary Association (LAVA), UK*
Medical Research Council, UK*
Monkey Sanctuary Trust, UK
National Council of Women of Great Britain*
Naturewatch, UK*
Office of the Chief Rabbi, UK
Parkinson's Disease Society, UK*
Pfizer Global R&D, UK
Roslin Institute, UK
Royal Society, UK*
Royal Society for the Prevention of Cruelty to Animals (RSPCA), UK*
Society for Accountability of Animal Studies in Biomedical Research and Education (SABRE), UK*
Uncaged Campaigns, UK*
Universities Federation for Animal Welfare, UK*
University of Leeds, Ethical Review Process, UK
Wakefield Research Ethics Committee, UK*
Wellcome Trust, UK*
World Society of the Protection of Animals

***Individuals***
Anonymous (9)
Dr Syed Khawar Abbas, Veterinary Officer, University of Leeds, UK
Taimoor Agha, UK
Sahar Akhtar, Economist, Duke University, USA
Stuart Andrews, UK*
Gaynor Armitage, UK*
Results of a debate held with pupils from various schools (held at the science centre @ *Bristol*)*
Professor Michael Balls, Chairman of the FRAME Trustees, UK*
Ms Claire Batchelor, UK
Professor Vera Baumans, The Netherlands*
Ms Sue Baumgardt, UK*
Dr Angus Bell, UK
Dr Eva Berriman, Australia*
Dr Nikola Biller-Andorno, Switzerland*
Professor Julian Blow, UK*
A J Bowater, UK
Ms Sandra Brooks, UK
Nicola-Daniel Cangemi, Council of Europe
John Card, Australia*
Mr Shaun Carey, UK
Mr Chris Childe, UK
Miss Lisa Coker, UK
Mr Tony Cooke, UK*

Patrizia Costa, Italy
Mrs Heather Cox, UK*
Norman Cox and Patricia Cox, UK
Dr James Crissman*
Professor David DeGrazia, USA
Mr Paul Dove, UK*
Karl Drinkwater, UK
Phillip Duckworth, UK*
Ms Paula Dyer, UK*
Gareth Edwards, National Animal Sanctuary Alliance, UK*
Mrs Sheila Edwards, United Arab Emirates
Mrs Tabitha Evans, Pharmaceutical Scientist, UK*
Mr Alan Fairhurst, Wistaston Cat Refuge, UK*
Ms Linda Freston, UK*
Professor Peter Furness, UK
Mr Joe Gernatowski, UK
Mr Francis H Giles*
Suzie Green, UK*
Elizabeth Gyimah, UK
Caro Hall, UK*
Professor Bernie Hannigan, UK
Claire Hardman and Tom Schoeffler, Australia*
Dr Nancy Harrison MD, USA*
Mr Simon Hartley, UK*
G Hawkins
Mr K Hill, UK*
Ms Olga Hill, UK*
Cris Iles-Wright, UK*
Dr Chris Jackson, UK
Lindsay Jackson, UK
Dr Brigitte Jansen, Germany
Ms Sarah Johnson, National Institute for Medical Research, Medical Research Council, UK
Frank A Jones
Dr Klaus Kallenbach, Hannover Medical School, Germany
Dr Stephen R Kaufman MD, USA
Dr M Kiley-Worthington, Eco Research and Education Centre, France
Andrew Patrick Kirk, UK
Mr Kedarraja Kistnareddy, UK
Ms Lynda Korimboccus, UK*
L Lougheed, UK*
Ms Pamela Lunn, UK
Hochong Man, UK
Miss Sophia Marsden, UK

Steve Mathew, UK
Member of North Wales Central Research Ethics Committee, UK
Ms Geeja Mohamed, UK
Professor David B Morton, UK
James Newton, UK
Dr Finbar O'Harte, UK
Miss Amy Oladeji, UK
Mr Derek S Paton, Dundee Animal Rights, UK
C R Pearson, UK
Dr Katherine Perlo, Dundee Animal Rights, UK*
Ms Vivien Pomfrey, UK*
Dr Pandora Pound, UK*
Mrs Diana Pullin RGN, HIV Field
Mr David Quirk, UK
Rosamund Raha, UK*
Professor Tom Regan, USA*
Professor David B Resnik, USA*
Dr RM Ridley and Dr HF Baker, UK*
Lesley Roberts
Ms Wendy Rooke, UK*
Neil Rothwell, UK*
Mrs GD Russell, UK*
Roger Scruton, Horsell's Farm Enterprises, UK*
Mr Philip Senior, UK*
Smadar*
Emily Smith, UK
Mrs Sarah Smith, UK
Lord Soulsby, UK*
Mr Alan St. John, UK*
Mohamed Sultan, UK
Nancy Swinnen, UK
Axel Thomson
Mrs Patricia Townsend, UK*
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# Glossary

**Absolutism:** The acceptance of or belief in absolute principles in political, philosophical, ethical, or theological matters.

**Ascites:** The accumulation of fluid in the abdominal cavity causing swelling.

**Adjuvant:** A substance which enhances the body's immune response to an **antigen**.

**Adrenal cortex:** Part of adrenal gland which is involved in making steroid **hormones** such as **cortisol**.

**Alternatives:** An alternative is likely to mean *an alternative method that does not involve using an animal*. This is the principle encompassed by UK and EU laws.

**Amino acid:** A molecule which serves as the building block of **proteins**. Proteins have different characteristics as determined by the sequence of amino acids. **Genes** specify this sequence.

**Anaesthesia:** Artificially induced loss of consciousness or sensation.

**Analgesia:** The absence or relief of pain.

**Analgesic:** A pain relieving medicine.

**Anaphylaxis:** An extreme and often life-threatening immune reaction to an **antigen**, such as a bee-sting, owing to hypersensitivity following an earlier exposure.

**Antibody:** A class of **proteins** made by the immune system which react with and neutralise specific foreign **antigens** (any substance recognised by the immune system as 'non-self').

**Antigen:** A foreign substance or **cell** that triggers an immune response. Its capacity to produce an immune response is referred to as its antigenicity.

**Assay:** the determination of the content or concentration of a substance.

**Ataxia:** An inability to coordinate muscular movements.

**Autoimmune disorder:** A malfunction of the immune system in which it responds against substances and **cells** naturally present in the body (of animals or humans).

**Base pair:** A pair of complementary components (called bases) in the two opposing strands of **DNA**.

**Basic research:** Research with the primary purpose of advancing scientific knowledge about the way animals behave, develop, or function. Also known as 'blue-sky' or 'curiosity-driven' research.

**Bioavailability:** The degree or rate at which a **drug** or other substance is absorbed and becomes available at its site of action in the body after administration.

**Biopharmaceutical:** Medicinal **drugs** produced by biotechnology.

**Blastocyst:** A very early stage **embryo**.

**Carcinogenicity:** Capacity of a substance to cause cancer.

**Cell:** The structural and functional unit of which organisms consist.

**Cell line:** A population of **cells** that can proliferate indefinitely in a culture dish.

**Cell culture: Cells** maintained in a culture dish.

**Cetaceans:** Order of marine mammal which comprises whales and dolphins.

**Chimera:** An organism made up of **cells** derived from two genetically distinct organisms.

**Chromosome:** A large **DNA** molecule and its associated proteins in the nucleus of a cell. Genes are specific sequences within the **DNA** molecule.

**Circadian:** Occurring or recurring about once per day.

**Cloning: Gene** cloning is the process of amplifying (making further copies of) a single gene sequence. Animal cloning is the process of producing virtually genetically identical animals (clones).

**Consequentialism:** A philosophical approach by which the moral value of individual human actions, or rules for such actions, is determined primarily by their outcome.

**Cortical:** Of or relating to the cerebral cortex.

**Cortisol: Hormone** produced by **adrenal cortex**, which is often used to assess the degree of stress in an animal.

**Cytotoxicity: Toxicity** to **cells**.

**Deontology:** Philosophical theory in which certain actions are right or wrong independent of their outcome. Instead, their rightness or wrongness is defined by a formal system, which defines certain actions as intrinsically right or wrong.

**Disease phenotype**: The observable characteristics of a disease.

**DNA:** Deoxyribonucleic acid; genes are specific regions within the DNA molecules that control the inherited characteristics of an organism.

**cDNA (Complementary DNA):** single-stranded **DNA** produced from messanger **RNA** sequences, which means that it contains only the sequences that code for **proteins**.

**Drugs:** Medicinal substances.

**Efficacy:** The ability to produce a particular desired effect.

**Embryo:** An early stage of animal or plant development.

**Endocrine system:** A system of glands in the body and the secreted **hormones** that they produce.

**Endogenous opioid:** Morphine-like substance which is made naturally within the body.

**Endpoint:** The stage in an **experiment** or test where the **procedure** is terminated. Where **experiments** increase suffering, animals should be killed as early as possible. This is described as operating a '**humane endpoint**'.

**Etiology:** The study of the causes of disease.

**Euthanasia:** Literally: 'good death'. The act of killing a human or other animal in as painless a way as possible.

**Experiment:** Part of a methodological research project with the aim of answering a particular theoretical question.

**Fecundity:** Fertility, the capacity for producing offspring.

**Fibroblasts:** A common **cell** type found in **vertebrate** animals. They are commonly used in experiments, as they proliferate freely in culture.

**Gene:** A region of **DNA** that controls an inherited characteristic of an organism.

**Gene expression:** The process by which information contained in a **gene** is transcribed to produce functional **RNA** molecules, which are then translated into **proteins**. Only a subset of an organism's genes are expressed in any one **cell** type.

**Genotoxicity:** Damage to **DNA**, which may promote the development of cancer or, if it involves the gametes, cause heritable **mutations**.

**Genetics:** The inheritance of variation.

**Genetic modification:** The modification of an organism's hereditary material using scientific techniques, (also known as genetic engineering).

**Genetic screen:** A search through a large number of intentionally created **mutant** organisms for a particular observable characteristic of scientific relevance.

**Genome:** The total **genetic** complement of a **cell**, individual, or species, which is contained in its **DNA**.

**Genomics:** The science of studying the **DNA** sequence and properties of entire **genomes** (the **sequencing** of the DNA of the entire human genome is an example).

**Genotype:** The entire genetic constitution of an individual, as distinguished from their observable characteristics (which are referred to as their **phenotype**).

**Germline:** The **gametes** (eggs or sperm) and the **cells** that give rise to the gametes, which transmit genetic material from one generation to the next.

**Great apes**: An order of primates consisting of gorillas, chimpanzees, bonobos and orangutans.

**Hepatocyte:** The main specialised **cells** of the liver.

**Hepatotoxicity:** Damage to the **hepatocytes** of the liver.

**Histopathology:** Cellular changes in **tissues** caused by disease.

**Hormone:** A molecule secreted by an **endocrine** gland into the blood that regulates the development and/or activities of specific **cells** in the body.

**Humane endpoint:** See **Endpoint**.

**Hybrid:** A hybrid animal or plant is the product of a **genetic** cross between two different breeds, lines or species; species hybrids such as mules are often sterile. Hybrid cells can be produced in culture by fusing two different **cell** types.

**Hybrid view:** A view that combines two different viewpoints.

**Immunodeficient:** An animal with a poorly functioning immune system.

**Inbred strains:** Organisms that are almost **genetically** identical, which are usually produced by repeated rounds of inbreeding.

**Incubation period** (of a disease): The period between exposure to an infection and the appearance of the first symptoms.

**Intravenous (i.v.):** Administered into a vein.

**Invasive:** A **procedure** that involves the introduction of instruments into the body.

**Invertebrates:** Animals without a backbone.

***In vitro*:** A process or **procedure** in a test tube or culture dish ('in glass').

***In vivo*:** A process or **procedure** in a living animal ('in life').

**Kantian:** Approach of the German philosopher Kant. Kant affirms the existence of an absolute moral law, the categorical imperative. See **deontology**.

**Knock-out:** Removal or inactivation of a **gene**.

**Knock-in:** Replacement of one **gene** by another (often modified) gene.

**Locus:** (pl. loci) The site of a specific **gene** on a **chromosome**.

**Lymphocyte:** A type of white blood cell that is responsible for adaptive immune responses.

**Metabolic/metabolism:** The basic chemical processes that occur in a living organism or **cell**.

**Microelectrode:** A very small electrode, often used to study electrical characteristics of living **cells** and **tissues**.

**Mitochondria:** Organelles (specialised microscopic structures within a **cell**) involved in energy production in cells.

**Multigene families:** Groups of related **genes**. Multigene families are believed to have arisen by duplication and variation of a single ancestral gene.

**Mutagen:** A substance capable of causing a **mutation**.

**Mutation (or mutagenesis):** The chemical modification of a **DNA** sequence that has the potential to lead to a change in the function of a **gene**. Mutations may be caused either by mistakes during the copying of DNA during **cell** division or by exposure to DNA-damaging agents in the environment. Mutations can be harmful, beneficial, or, most commonly, of no consequence. They are only inherited if they occur in **cells** that make eggs or sperm.

**Neural:** Of or relating to the nervous system.

**Neuron:** A nerve **cell**.

**Neurotransmitter:** A chemical substance released from a nerve cell that signals to another nerve or muscle cell at a specialised contact site called a synapse.

**Nociception:** The registration, transmission and processing of painful stimuli by the nervous system.

**Nuclear transplantation**: Transplantation of a **nucleus** from one **cell** into another cell from which the **nucleus** has been removed.

**Nucleus:** (pl. nuclei) A large, membrane-enclosed organelle in an eukaryotic **cell**, containing the **chromosomes**.

**Nucleotide:** The subunits from which **DNA** and **RNA** molecules are assembled. A nucleotide contains a base molecule (adenine, cytosine, guanine or thymine in DNA; adenine, cytocine, guanine or uracil in RNA), linked to a sugar molecule and phosphate groups. Specific sequences of three nucleotides code for specific **amino acids**.

**Nude mouse:** A mutant mouse strain that arose spontaneously, which has no fur or thymus gland. Because it has no thymus, it is **immunodeficient**, and will readily accept foreign **tissue** grafts.

**Old world monkey:** A group of primates distinguished by their non-prehensile (incapable of grasping) tails.

**Olfaction:** The process of smelling.

**Ontology:** A branch of metaphysics dealing with the nature of being. The term is also used to describe the relationship between different terms in formal structures, or the principles underlying the organisation of systems such as databases.

**Oocyte:** An immature **germ** cell that matures into an egg.

**Over-expression:** Greater than normal production, for example, of a **protein** or **RNA** molecule from a **gene**.

**Patagial:** The wing membrane of a bat or similar animal.

**Pathogen:** An agent causing disease.

**Pathogenesis:** The processes by which a disease develops.

**Peptide:** A short string of **amino acids**, which occurs either within a larger **protein** molecule or as an individual, biologically important molecule.

**Peritoneum:** The cellular membrane lining the cavity of the abdomen (the peritoneal cavity).

**Pharmaceutical:** Medicinal **drug**.

**Pharmacokinetics:** The process by which a medicine is absorbed, distributed, metabolized and eliminated by the body.

**Pharming:** The production of **pharmaceuticals** in **genetically modified** plants or animals.

**Phenotype:** The observable or measurable traits of an individual, which depend on both its **genotype** and the environment.

**Phototoxicity: Toxicity** of a compound in the presence of light. While a medicine by itself may have no toxic effects, this may change in combination with light.

**Potency:** Strength of action.

**Prion:** Infectious **proteins** that are the cause of transmissible spongiform encephalopathies such as scrapie, BSE and CJD.

**Procedure:** A combination of one or more technical acts carried out on an animal for an **experimental** or other scientific purpose which may cause that animal pain, suffering, distress or lasting harm. The Animals (Scientific Procedures) Act 1986 uses the term 'procedure' rather than '**experiment**' so that laboratory animals used in ways which are not experimental, such as breeding of harmful mutants, are also covered.

**Progeny:** The offspring of an organism.

**Prophylactic:** For the purpose of preventing disease.

**Protein:** A molecule consisting of a long chain of **amino acids**, folded up into a specific three-dimensional structure, which determines its function. Proteins are encoded by genes and are essential for almost all life processes.

**Pyrogenic:** Producing heat, especially in the body.

**Receptor:** A molecule on or in a **cell** that specifically recognises a signal molecule outside the cell such as a **neurotransmitter** or **hormone**.

**Retro-orbital bleeding:** A method of drawing blood from behind the eye.

**Ribonucleic acid (RNA):** A single stranded nucleic acid molecule produced by transcription from **DNA**. It consists of a long chain made from four **nucleotides**, whose sequence determines the informational content of the molecule. It may either be translated into **protein** or may itself have a direct functional role.

**Ruminant:** A hoofed animal that chews the cud e.g. cows, sheep.

**Selective breeding:** Where organisms exhibiting desired characteristics are used to produce offspring that also bear those characteristics.

**Sentient:** Having the power of perception by the senses.

**Sequencing:** Ascertaining the sequence of **amino acid** subunits in a polypeptide (**protein**) or of **nucleotides** in an **RNA** or **DNA** molecule.

**Somatic:** Of or relating to the body. A distinction is often made between the somatic cells of an animal, which leave no **genetic** trace when the animal dies, and the **germ** cells, which can pass on the animal's genetic information to the next generation.

**Stem cells:** Undifferentiated **cells**, which can divide indefinitely and produce either more stem cells or cells that commit to becoming more specialised (differentiated) cell types.

**Stereotypy:** A repeated, relatively invariant sequence of movements that have no obvious function.

**Stroke:** A sudden disabling attack or loss of consciousness caused by either an interruption in the flow of blood to the brain or bleeding into the brain.

**Subcellular:** Situated or occurring within the **cell**.

**Synovium:** The cellular membrane lining joints.

**T cells: Lymphocytes** of the immune system that derive from the thymus gland. They make cell-mediated immune responses rather than **antibody** responses.

**Telemetry:** The automatic measurement and transmission of data by radio or other means from remote sources. This is used for recording and analysis.

**Teratogenicity:** Capacity to cause malformations of an **embryo**.

**Three Rs:** Reduction, refinement, replacement.

**Tissue:** Any of the coherent collections of specialised **cells** of which animals or plants are made, such as muscular or vascular tissue. Tissues are combined to make organs, such as the brain and liver.

**Tissue culture: Tissues** maintained in a culture dish.

**Toxicity:** Capacity to cause harm to **cells** or organisms.

**Toxicogenomics:** A scientific sub-discipline concerned with the influence of genes in determining susceptibility to specific toxins.

**Transgenic animal:** An animal that has been **genetically modified**.

**Utilitarianism:** A form of **Consequentialism**. The philosophy states that the best actions are those that produce most overall happiness or pleasure.

**Vaccine:** An antigenic preparation used to stimulate immune responses in order to protect an individual against a disease —usually an infectious disease. Experimental vaccines to treat some cancers are being tested in trials.

**vCJD (variant CJD):** A form of transmissible spongiform encephalopathy in humans caused by BSE **prions**.

**Vertebrates:** Animals with a backbone.

**Virulent:** (of a **pathogen**) capable of causing serious disease.

**Wild type:** A form of an organism, strain, **gene**, or characteristic, as it occurs in nature.

# Glossary of abbreviations

| | |
|---|---|
| **3Rs** | Reduction, Refinement and Replacement |
| **ABPI** | Association of the British Pharmaceutical Industry |
| **ADR** | Adverse drug reaction |
| **AIDS** | Acquired Immune Deficiency Syndrome |
| **ALF** | Animal Liberation Front |
| **AMRC** | Association of Medical Research Charities |
| **APC** | Animal Procedures Committee |
| **A(SP)A** | Animals (Scientific Procedures) Act 1986 |
| **BBSRC** | Biotechnology and Biological Sciences Research Council |
| **BMA** | British Medical Association |
| **BSE** | Bovine Spongiform Encephalopathy |
| **BUAV** | British Union for the Abolition of Vivisection |
| **CJD** | Creutzfeld-Jakob Disease |
| **CMP** | Coalition for Medical Progress |
| **CNS** | Central nervous system |
| **CSM** | Committee on Safety of Medicines |
| **DBS** | Deep brain stimulation |
| **DNA** | Deoxyribonucleic acid |
| **DTI** | Department of Trade and Industry |
| **EC** | European Commission |
| **ECG** | Electrocardiogram |
| **ECVAM** | European Centre for the Validation of Alternative Methods |
| **ERP** | Ethical Review Process |
| **ES Cells** | Embryonic stem cells |
| **EU** | European Union |
| **FDA** | US Food and Drug Administration |
| **FoI** | Freedom of Information Act |
| **FRAME** | Fund for the Replacement of Animals in Medical Experiments |
| **GM** | Genetically modified |
| **HIV** | Human Immunodeficiency Virus |
| **HO** | Home Office |
| **HSE** | Health and Safety Executive |
| **IAT** | Institute of Animal Technology |
| **ICCVAM** | Interagency Co-ordinating Committee on the Validation of Alternatives |
| **ICH** | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| **IDG3Rs** | Inter-departmental Group on the 3Rs |
| **LAVA** | Laboratory Animal Veterinary Association |
| **LASA** | Laboratory Animals Science Association |
| **MAG** | Myelin-associated glycoprotein |
| **MHRA** | Medicines and Healthcare products Regulatory Agency |
| **MORI** | Market & Opinion Research International |
| **MRC** | Medical Research Council |
| **MRI** | Magnetic Resonance Imaging |
| **NACWO** | Named Animal Care and Welfare Officer |

| | |
|---|---|
| **NAVS** | National Anti-Vivisection Society |
| **NC3Rs** | National Centre for the 3Rs |
| **NVS** | Named Veterinary Surgeon |
| **OECD** | Organisation for Economic Cooperation and Development |
| **OTMS** | Over thirty months scheme |
| **PET** | Positron Emission Tomography |
| **RA** | Rheumatoid arthritis |
| **REACH** | Registration, Evaluation and Authorisation of Chemicals |
| **RDS** | RDS: Understanding Animal Research in Medicine. Previously the Research Defence Society |
| **RNA** | Ribonucleic acid |
| **RSPCA** | Royal Society for the Prevention of Cruelty to Animals |
| **SHAC** | Stop Huntington Animal Cruelty |
| **The *Statistics*** | Home Office (2004) *Statistics of Scientific Procedures on Living Animals Great Britain 2003* (Norwich: HMSO) |
| **TNF** | Tumour Necrosis Factor |
| **TSE** | Transmissible Spongiform Encephalopathies |
| **UFAW** | Universities Federation for Animal Welfare |
| **USA** | United States of America |

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Published March 2005

NUFFIELD COUNCIL ON BIOETHICS

Published by
Nuffield Council on Bioethics
28 Bedford Square
London WC1B 3JS

Telephone: + 44 (0)20 7681 9619
Fax: +44 (0)20 7637 1712
Internet: www.nuffieldbioethics.org