The APC
Animal Procedures Committee

ANIMAL PROCEDURES COMMITTEE

REVIEW OF COST-BENEFIT ASSESSMENT IN THE USE OF ANIMALS IN RESEARCH

JUNE 2003

PREFACE

Letter to the Minister from Michael Banner, Chair of the Animal Procedures Committee

17 June 2003

Dear Ms Flint

ANIMAL PROCEDURES COMMITTEE: RECOMMENDATIONS ON COST-BENEFIT ASSESSMENT UNDER THE ANIMALS (SCIENTIFIC PROCEDURES) ACT 1986

On behalf of the Animal Procedures Committee I enclose the Committee's report on cost-benefit assessment. In it we address the adequacy of the current cost-benefit assessment performed in the course of evaluating project licence applications. We have sought to look at the many issues which arise in relation to this important element of the regulation of the use of animals, but would draw attention to three particular aspects of our work.

In the first place we have addressed the fundamental question as to scientific validity of the use of animals. We believe that our considerations and conclusions offer an important clarification of the debate and fulfil the request made by your predecessor, Mike O'Brien, to provide advice on this issue.

Secondly, while we conclude that some uses of animals may yield scientific knowledge, we argue that this does not settle the question of justification. We go on to elucidate the full range of factors which must be considered for there to be a rigorous application of the cost-benefit assessment.

Thirdly, we also consider how the practice and process of cost-benefit assessment can be enhanced so that it can be, and be seen to be, critical and comprehensive. This includes a discussion of the future use of the severity limit and band labels, as you requested of the APC in your letter of 10 February 2003.

It is important that I should stress that our report does not issue in a series of neat recommendations, but in a challenge to all involved in this field to engage in the sort of critical, imaginative and creative thinking which will be required if we are to make the progress in this difficult area. For many people the use of animals is thought of as a regrettable necessity; in that context, there can be no satisfaction with the status quo, but only a determination to consider what steps can be taken, compatible with legitimate scientific progress, to avoid or reduce animal suffering.

I commend this report to you and hope that the APC can play a part, with others, in taking forward thinking and practice in this area

Sincerely
MICHAEL BANNER

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GLOSSARY

ACRONYMS USED IN THIS REPORT

ABPI	The Association of the British Pharmaceutical Industry
APC	Animal Procedures Committee
ASPA	The Animals (Scientific Procedures) Act 1986
AVTRW	Association Of Veterinary Teachers And Research Workers
BUAV	British Union for the Abolition of Vivisection
BVA:AWF	British Veterinary Association: Animal Welfare Foundation
CNS	Central nervous system
EPA	US Environmental Protection Authority
ERP	Ethical Review Process
EU	European Union
FDA	US Food and Drug Administration
FRAME	Fund for the Replacement of Animals in Medical Experiments
LASA	Laboratory Animal Science Association of the UK
HSE	Health and Safety Executive
MRC	Medical Research Council
NACWO	Named Animal Welfare Care Officer
NAVS	National Anti-Vivisection Society
NVS	Named Veterinary Surgeon
OECD	Organisation for Economic Cooperation and Development
PSD	UK Pesticides Safety Directorate
RSPCA	Royal Society for the Prevention of Cruelty to Animals
UFAW	Universities Federation for Animal Welfare
UKLSC	UK Life Sciences Committee
USDA	US Department of Agriculture

CHAPTER 1

INTRODUCTION AND METHODOLOGY

1.1 The Animal Procedures Committee

To begin our report it will help to set out some basic information about how animal experimentation is controlled in the UK; what the Animal Procedures Committee (APC) is; and what it does.

The APC was first appointed in 1987 and was set up by Sections 19 and 20 of the Animals (Scientific Procedures) Act 1986 ('the Act'). This Act requires the licensing of any experiment or other scientific procedure carried out on living, protected animals which may cause them pain, suffering, distress or lasting harm. It regulates scientific procedures carried out on all vertebrate species except man - that is mammals, reptiles, birds, amphibians and fish - and one invertebrate species, *Octopus vulgaris*.

The Act applies throughout the United Kingdom. For work taking place in England, Scotland and Wales the Home Office issues licences under the Act on behalf of the Home Secretary. In Northern Ireland, licences are issued by the Department of Health, Social Services and Public Safety. Both departments have Inspectorates consisting of professional staff with medical or veterinary qualifications who examine and advise on all applications for authorities under the Act. They also inspect establishments and the licensed work being carried out there.

The function of the Animal Procedures Committee is to provide the Ministers with independent advice about the Act and their functions under it. The Home Secretary in practice delegates his responsibilities for animal experimentation to another Home Office Minister. In Northern Ireland the Act is the responsibility of the Northern Ireland Office. Whatever issue the Committee is looking at, the law requires it to take account both of the legitimate requirements of science and industry and of the protection of animals against avoidable suffering and unnecessary use in scientific procedures.

1.2 Background to this review

Ten years after the implementation of the Act, the APC conducted a review of its operation, which was published in the Annual Report for 1997. As that report explains, we received during the course of the review a large number of comments about the cost-benefit assessment. It is a legal requirement that in determining whether and on what terms to grant a project licence to carry out scientific procedures on animals the Secretary of State is required to 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 (Section 5(4) of the Act). That process of weighing the adverse effects against the benefits is known as the cost-benefit assessment. It follows that "cost" does not refer to financial cost. The comments received in the course of the Committee's review of the Act showed that many believed that the cost-benefit assessment had made a contribution to animal welfare since the Act first brought it into law, but that some thought that the law was not applied with sufficient rigour. More generally there was some uncertainty about how the cost-benefit assessment operated in practice - uncertainty, regarding the factors that are taken into account and how these are put together in coming to a judgement. We concluded then that we should "produce and publish an extended statement on the assessment of costs and benefits required by the Act". We hoped that this would make an important contribution to the effective operation and public understanding of the principles and functioning of this significant piece of legislation.

The APC therefore decided to form a cost-benefit working group to take this work forward.

1.3 The Cost-Benefit working group

The Cost Benefit working group is chaired by Professor Michael Banner (Chairman of the APC and FD Maurice Professor of Moral and Social Theology, King's College, London), and its other members are Professor David Clark (Honorary Senior Research Fellow, University of Kent), Professor Alan Holland (Professor of Applied Philosophy, University of Lancaster), Dr Maggy Jennings (Head of Research Animals Department, Royal Society for the Prevention of Cruelty to Animals) and Professor John Martin (Professor of Cardiovascular Medicine, University College, London). The working group also employed a consultant, Dr Jane Smith, to carry out analysis and initial drafting of several sections of the report. We wish to register our gratitude to Dr Smith for her hard work, which was delivered to a demanding timetable. The working group was also grateful to the Animals (Scientific Procedures) Chief Inspector for his helpful contributions to our understanding of the issues.

Originally, the working group's terms of reference set by the main Committee were to

- compare the way the cost-benefit assessment is currently carried out with other cost-benefit models;
- investigate the factors that are, or should be, taken into account in the assessment of costs and benefits, and the relative weights applied to each, taking into account not only the individual project but how that project contributes to wider programmes of research and to the development of technology and human knowledge; and
- examine the nature of the judgement required when weighing costs and benefits, and how this judgement can be made more transparent and objective.

Later, the working group also took account of the views of the then Home Office Minister responsible for animal procedures, Mr Mike O'Brien, and decided also to produce an authoritative statement on the validity of animal experiments, and to address the question of whether and how the present cost-benefit assessment process might be improved.

The first meetings of the Working Group took place in 2000, and draft consultation letters were discussed with the full Committee. The agreed letter of consultation was sent out on 6 December 2000 and a press release announced it. A full list of those sent the consultation letter was circulated to the APC membership in order to identify any omissions, and the letter was also given wider circulation by being displayed on the Committee's website. The full text of the letter is attached at Annex A. A total of 340 responses were received from a wide variety of groups and individuals. Annex B is a list of all those who responded, but omits those who asked for their identities not to be disclosed.

Each member of the working group was provided with copies of all the written responses which had been received. Each response was read and was individually considered by the working group at its meetings. The discussion in the chapters which follow is both informed by the responses and designed to present the main issues and arguments raised. However, no attempt is made to provide a statistical analysis of these responses.

During 2001 the working group met on five occasions and in 2002 it met on 9 occasions. The working group presented a draft report to the main Committee at its meeting in October 2002.

CHAPTER 2

MORAL ISSUES

2.1 Introduction

Hardly anyone believes that the use of animals for the purpose of scientific experiment is a matter of moral indifference. It follows that such work stands in need of justification. It is upon this vitally important common ground that the Act is built. In particular, it is the fact that the infliction of suffering always requires justification that explains one of its central elements – the requirement that the Secretary of State shall weigh the likely adverse effects on the animals against the benefit likely to accrue as a result of the programme to be specified in the licence. One purpose of this Chapter is to identify the more common, and sometimes divergent, moral perspectives that people bring to bear on the issue of animal experiments. Another is to illuminate the considerations that provide the rationale for the Act and its structure. Our commentary is based both upon the responses that we received to the consultation document, and upon our perception of views that are held in society at large. One general finding is that there is undoubtedly a wide spectrum of views, rather than the simple polarisation that is so often depicted. Although we offer comment on various arguments and perspectives, it is not our purpose to attempt any final adjudication between these.

One respondent, for example, was very clear that "the purpose of the Act is not to facilitate scientific research but to protect animals" (The Boyd Group). We take this to imply the view that in granting a licence for animal research, society is not recognising a general right to perform such experiments, but recognising only that there may be circumstances when such experiments are morally defensible. A number of research establishments themselves seem to endorse this view, when they insist that they see their work with animals as a "privilege, not a right".

Several responses, however, seem to reflect a second, and different view. From one religious perspective came the response that animals are on this earth, among other reasons, to serve the needs of mankind. And a secular version of the same response seems to underlie the claim of one medical research charity that "everyone... has the right to benefit from the most up-to-date treatment to ensure that they live long and healthy lives" (British Heart Foundation). Both responses appear to reflect the view that animal research is, or should be, a generally permissible pursuit, and that the purpose of regulation in this area is to ensure that it is carried forward in the most humane way.

The differences between these two points of view are far-reaching: they imply a disagreement about the onus of proof, and they envisage different futures. One sees animal research as a 'necessary evil', and looks forward to a future in which such research no longer needs to be done: "I would really rather not do a single more animal experiment in my life. I love animals and respect them... I also love and respect human beings" (Anon.). The other standpoint appears to rest comfortably with a future in which research on animals continues indefinitely, as long as it is necessary for the benefit of mankind.

These diverging points of view generally reflect deep-seated philosophical disagreements about the nature of the differences between humans and other animals. From one perspective, humans are conceived as having a 'special' moral status, different in kind from that of other animals. This view is often said to be based on a religious belief such as the belief that humans are created in the image of God. But the view can also be supported by other – secular – considerations. For example, it

is sometimes urged that self-consciousness brings very special sensitivities – and vulnerabilities - into play. It implies, for example, a unique awareness and anticipation, both of suffering and of death. Many take the view that this gives human demands a claim to override all other demands.

From another perspective, either it is denied that there are any morally relevant differences between humans and other animals, or it is claimed that these are only differences of degree. Therefore, legislation designed to protect human vulnerabilities should be extended to protect animals also. Some go further, and argue that animals have a right to such protection. Unfortunately, although the concept of rights was brought to bear in several responses, it appears that philosophical discussion of the issue of 'animal rights' is not sufficiently settled to provide clear guidance on the issue. Moreover, even if it were settled that animals do, or do not, have rights, it is not clear that this would resolve the specific issue of animal research, which turns on what rights animals do or do not have, and on how the rights of animals should be weighed in relation to the rights of humans. The language of 'rights' offers an alternative way of formulating the issues; it does not offer a way of settling them. Many pet-owners, for example, would concede that they have an obligation to feed their pets, and that the animals in turn have a 'right' to be fed. But this 'minimalist' view of rights would not settle whether they also have a right not to be the subject of scientific experiments.

One respondent puts the question in an interestingly different way. They ask "what right have we to experiment on animals?" (Anon.). The question deserves to be taken seriously. If the basis for claiming that animals have a right not to be subject to experimentation is obscure, the basis for the claim that humans have a right to perform such experiments is hardly less so. Certainly we cannot infer the presence of such a right on the part of humans from the denial of rights to animals. (By analogy, no right exists for a person not to be killed accidentally. It doesn't follow that others have a right accidentally to kill them.) If this is true, it would help explain the character of the legislation: in the absence of any such right, justification must be provided.

The same respondent adds that "injuries inflicted on animals during animal experiments would be illegal in any other context". This is by no means true of all such 'injuries', but it is true of many, at least. With respect to an issue raised above this fact would certainly suggest that experiments on animals are seen as having the legal, and perhaps moral, status of exemptions, or special permissions, and not as something that any member of society should consider they have a moral right to do: a licence is not "an intrinsic right... the issue of attitude is also important" (Anon.). Another factor pointing in the same direction is the widespread support for, and consensus around implementation of the Three Rs –

> **replacement** of sentient animals with insentient alternatives,
> **reduction** in the number of animals used to gain information of a particular amount and precision, and
> **refinement** of experimental procedures to reduce the incidence and severity of procedures on those animals that are still used following application of the previous two Rs (Russell and Burch 1992).

We presume that these objectives apply not simply in the sense that the numbers of animals used in any given project should be kept to a minimum, but also and crucially in the sense that it should be the aim of animal-related research in general ultimately to eliminate the need to use animals, at least for experiments that involve the infliction of significant amounts of suffering.
It is evident that procedures that inflict injury on

animals for reasons other than their own good require robust defence. Mostly, the reasons why such defence is required are of the very same kind that make people contemplate the experiments in the first place. It is increasingly rare to encounter scientists who would deny that vertebrate animals generally (and this of course includes humans) are sentient subjects of a life who possess a range of cognitive faculties and affective states, and that, for mammals at least, these include expectation, fear, memory, desire, frustration and a variety of social and psychological needs.

Animal suffering and human need are clearly key matters of concern. But some respondents suggested that two other values have potential relevance also. The first of these is justice. One respondent urged that humans should accept death and pain as a normal part of living. On one interpretation, this would seem needlessly severe. Most people would think it right, and even an obligation, to resist pain and death by all reasonable means. But the difficulty comes, of course, when we ask how far we should take this 'resistance'. The writer is perhaps appealing to some notion of natural justice, often appealed to in human affairs where it is felt that moral claims exist that go unrecognised in law. (Examples might include the issues surrounding pensions for war widows, or whether society is entitled to imprison people, literally, 'for life'.) Applied between species, it might be used to suggest that each species has its 'quota' of afflictions, and that it is unjust for humans to buy relief from their quota by imposing extra burdens on other species. The idea is not without interest, but unfortunately has proved difficult enough to sustain in its purely human applications, let alone the more ambitious cross-species application envisaged here.

The second value is autonomy, especially as exemplified in freedom of inquiry. Autonomy in general is, for many, an indispensable condition for a worthwhile life. A signal of its supposed importance is that there are some who choose death rather than face loss of autonomy. However, it is clear that no specific expression of autonomy e.g. freedom to conduct scientific research, can have such an overriding status. We accept restrictions on our autonomy in a whole variety of circumstances, most notably restrictions enshrined in law. And there is good reason for this – namely that autonomy is a competitive good in the sense that its enjoyment by one person can jeopardise its enjoyment by others. Neither autonomy, nor justice, it appears, can offer us clear direction in the area of animal research.

We can approach most of the issues raised by animal experimentation by considering:

- the rights and wrongs of the actions involved
- the worth, or otherwise, of the motivations
- the actual and/or potential consequences.

2.2 Action

Several respondents clearly felt that the issue of animal experiments was decidable on the basis of the inherent wrongfulness of the actions involved. One (typical) expression of this view was: "it is morally indefensible to knowingly inflict suffering on sentient animals" (British Union for the Abolition of Vivisection, BUAV). It would seem that we need to add two qualifications in order to make this view at least plausible. We need first to insert 'innocent' animals, since otherwise this would imply that the punishment of (human) criminals was 'morally indefensible'. We need also to add 'other than in their own interests' since we also, obviously, regularly approve of veterinary treatment for animals, including maybe painful surgery. Thus amended, the claim is that 'it is morally indefensible to knowingly inflict suffering on innocent sentient animals other than in their own interests'.

Even if this claim were accepted, it would not imply that animal experiments should never be carried

out. As pointed out in the APC Biotechnology Report (Home Office 2001, para. 44), actions that are inherently or intrinsically wrong are not therefore absolutely wrong, in the sense that there are no circumstances in which they could be justified. For example, an action that is judged to be wrong might nevertheless be justified if it could be shown to be the lesser of two wrongs that we have to choose between. Moreover, the claim does not seem to rule out experiments on animals provided that they are anaesthetised.

Even so, many would reject the claim and opt for the more permissive principle that informs current interpretations of the Act. Under the Act as it stands, and as further elaborated in the *Guidelines on the Operation of the Animals (Scientific Procedures) Act 1986* (Home Office 2000), certain actions are indeed precluded, presumably because they are judged morally indefensible, namely those that involve the infliction of severe or prolonged pain or distress: "The Secretary of State will not licence any procedure likely to cause severe pain or distress that cannot be alleviated" (Home Office 2000, para. 5.42, p. 32). But clearly, such a principle is more permissive, since it is compatible with the infliction of significant suffering on sentient animals.

The distance between these two positions may not seem enormous, and both reflect a common concern over animal suffering. Nevertheless, it is a significant point of divergence between those who support, and those who oppose, animal experiments.

In part, the disagreement may be attributed to differing interpretations of the actions of those who conduct such experiments. Those who disapprove may do so because they believe it is indefensible to use the suffering of one creature solely as a means by which to alleviate the suffering of another. Those who approve may do so because they see the primary purpose of such experiments to be the alleviation of suffering. The suffering of the animals is viewed, not as the means to this end, but as its anticipated consequence. To take such a view is to appeal to a version of what is known as the 'doctrine of double effect'. The classic example is that of a surgeon who, in saving a mother's life, terminates the life of a foetus by, for example, removing a cancerous womb. According to the doctrine of double effect, the death of the foetus is not the means by which the mother's life is saved, but the regrettable consequence of an otherwise defensible, even laudable, action – the removal of the cancerous womb.

A number of respondents focused on another feature of actions that is relevant to their justification – namely consistency. The specific point of comparison to which they drew attention was the raising, keeping and slaughtering of animals for food. One respondent put the point as follows: "we are quite content to kill 650 million animals per year for food in this country with, in some cases, quite marked suffering in life and at slaughter, yet it is suggested that we may not want to conduct experiments, on a much smaller scale, which provide a benefit, even if the animals do not suffer. This is not logical" (Anon.). Another respondent invites us to consider the comparison with 'pest' control, both as regards numbers of animals killed and the kinds of death they undergo, or the adventitious deaths that arise in connection with the various forms of transport, with commercial fishing, and so forth (Anon.). The claim is that we cannot, in all consistency, expect society to abandon animal research while it condones their slaughter, both for food, and for a variety of other reasons, some intentional, and some not.

It is true, of course, that many who oppose animal experiments also oppose their slaughter for food. But they don't appear to think that the abandoning of experiments must await the dawn of a vegetarian society. It is true also that the consistency point cuts both ways. If we really believe experimental animals are deserving of the care, attention and

environmental enrichment that is recommended by various codes of practice, then we ought to ensure the same for food animals. So the appropriate point of comparison should perhaps be with an 'improved' food animal industry. But the challenge remains: to show why a society that believes it defensible to kill large numbers of animals for food should refrain from using smaller numbers of animals for research, much of which is directed at improving and protecting human health.

The opponent of animal research might of course respond that the lesser assault cannot be justified by the mere fact of the greater assault, but requires its own independent justification. Another line of response might be to point out that whereas death is inevitable, suffering is not. So provided that death is humane, it does not add to the ills of the world, whereas the infliction of suffering – for whatever reason – does. This is perhaps the reason why, as the Medical Research Council (MRC) says: "society accepts the taking of animal life more freely than it accepts animal suffering".

Even so, the position of opponents of animal research – that even if the taking of life for food were acceptable, the use of animals for experimentation is not – appears in need of more thorough articulation if it is to carry conviction, not least because the differences between these two practices can seem vanishingly small. Food animals, for example, are not spared the anticipation of death, and their deaths are, in many cases, less controlled than those of laboratory animals. Moreover, all food animals undergo premature death, and therefore a form of loss, whereas some laboratory animals experience only relatively minor adverse effects and do not necessarily undergo premature death. On the other side of this debate, however, the claim was made that "the laboratory environment does not provide the environmental enrichment considered a minimum requirement for captive animals in other industries" (Northern Ireland Against Animal Experiments). The suggestion is that even though the laboratory environment is more strictly controlled, it starts out from a much lower base to begin with e.g. typically a cage rather than – say – a field. Moreover, that the mere fact of being confined in a cage constitutes a harm to the animals.

Two other points raised in defence of animal research should be briefly noted. One is the argument that researchers are entitled to take the lives of animals that they have created for the purpose of their research. In the words of one response: "the overwhelming majority of experimental animals would not have life were it not for their involvement in the experimental process" (The Royal College of Physicians and Surgeons of Glasgow). The general principle being appealed to here is not entirely clear. An appeal to some kind of 'creator's prerogative', at any rate, appears dubious. We do not, for example, think that parents have any more right than anyone else to harm their children, simply because they have created them. Nor is it obvious that the significance of an animal's life is confined to the purposes that humans have in mind for them.

The other is the argument that research animals lead better lives than their wild counterparts. As one response puts it: "in general, laboratory animals lead an idyllic life" (B & K Universal Ltd.). But in the first place, this remark seems to show a clear anthropomorphic bias. Whatever is meant by 'idyllic', it is far from obvious that it has any meaning from the animal's point of view. In the second place, even were it true that these animals fare as well as, or better than, their wild counterparts this cannot be taken as a standard for how, as humans, we should relate to them. The fact that a rabbit in the wild might be torn apart by a fox, for example, surely has no bearing on how we humans may or may not behave towards rabbits.

2.3 Motivation

Two conventional ways of characterising the debate about animal experiments appeal to the contrasting

motivations that are alleged to be involved. One, offered by some opponents of animal experiments, sees the issue in terms of a conflict between greed and compassion: e.g. "it's all to do with making money" (Anon.). The other, offered by some supporters of animal experiments, sees the issue in terms of a conflict between 'reason' and emotion. We find both of these characterisations problematic.

The problem with seeing the issue in terms of a conflict between greed and compassion is that this confuses individual motivations with publicly defensible justifications. It is the latter with which we should be concerned in considering the moral validity of animal experiments. And even if it were not, it needs to be noted that careers are at stake in animal protection organisations as well as in animal research organisations.

But even if we keep to publicly defensible justification, some commentators still find reason to be critical. They argue, for example, that the research that is actually carried out does not always match the research that most needs to be carried out, nor does it always pursue the objectives most commonly put forward as (generally) justifying such research. Even in a recently published defence of animal research – Why Animal Experimentation Matters (Paul and Paul 2001) – which makes great play of its potential in helping us combat some of the most seriously threatening diseases of our time, we find the admission that there are as yet "no vaccines and no cures" for the diseases caused by Marburg, Lassa, Ebola and HIV viruses. At the same time it is claimed that "today humans in the developed world enjoy unparalleled health and longevity" (p.42) – indicative, critics would argue, of where the research effort has actually been directed. A further point is that, given the variety of social and economic pressures, especially the pressure of commercial objectives, we do need to be constantly vigilant that the research proposed keeps within the limits of the allowable purposes prescribed by the Act.

The problem with seeing the issue of animal experiments in terms of a conflict between reason and emotion is that this fails to acknowledge the degree of feeling that lies behind support for animal research. The heart of the debate about animal experiments stems from the fact that as humans we are moved in different ways, and to different degrees, by the plight of both humans and other animals, not from the fact that some of us are emotional and some of us are not. Indeed, it would be rather appalling to think that those who conduct experiments on animals are not moved by feelings of compassion and sympathy for their fellow humans. And if there are purely 'rational' motivations for favouring such research, then so too are there 'rational' motivations for opposing it.

In considering the character and motivations of the human agents involved, therefore, it becomes particularly clear that the issue of animal research bears the classic hallmarks of moral conflict – conflict between two or more positions for which morally defensible arguments can be made. This appears especially true of research directed at the alleviation of human (and animal) suffering and the protection of human (and animal) health. Nor is the conflict by any means confined to that between different parties, or different interests. It is vitally important to bear in mind that this is a conflict that many people feel within themselves. Indeed, some of the most insightful responses to our consultation document reflected just such an inner conflict. At the same time, those who defend animal research can appeal precisely to this human susceptibility to moral conflict to underline their case for saying that the difference between humans and other animals is one of kind, rather than degree.

2.4 Consequences

There appears to be a general belief that under the Act, the justification for animal experiments is decided on exclusively consequential grounds – specifically by means of a 'cost-benefit assessment'. A detailed review of the kinds of costs and benefits

it is appropriate and proper to take into account is the subject of Chapter 4 of this report. Here we offer just a few general and preliminary remarks.

A first point to note, of some importance, is that this belief is not quite correct. It is true that the Act requires some form of 'cost-benefit assessment' to be carried out, but it only requires that the Secretary of State should 'take such an assessment into account', not that he or she should rely on it exclusively. In other words, the Secretary of State's decision is to be guided by, but not determined by, such an assessment. The point is important because it means that the Act does allow for non-consequential considerations to be taken into account.

A second point, as one respondent (The Boyd Group) correctly notes, is that the phrase 'cost-benefit assessment' does not actually appear in the Act. It is simply the phrase that has come into common use in discussion of the Act. We need to be particularly careful, therefore, to avoid two of its more misleading implications. The first is the suggestion that financial costs are somehow in play. We fully endorse the sentiment of another respondent (Anon.) that it would be quite unacceptable if the animal experiment option were chosen because it was cheaper. The second is the suggestion that the process is somehow quantifiable: "that there might be some universal formula that could be applied – if only someone were clever enough to discover it (or the Home Office would divulge it!)" (The Boyd Group).

So far as the issue of quantification is concerned, it is worth recording that there was very little support indeed, from any quarter, for a formulaic approach to the assessment of consequences. On the other hand, there was a great deal of support, from all sides, for the inclusion (in this report) of some illustrative guidance as to how such assessments are actually carried out. (For our response, see Ch. 5.)

Even setting aside the quantitative interpretation of cost-benefit assessment, however, some will still find difficulties of principle in applying this form of assessment to the case of animal experiments, thus putting their justification into doubt. Grounds for concern include the following:

- pain and pleasure (cost and benefit), it is claimed, are incommensurable: it is simply a mistake to imagine that they can be placed on any kind of continuum, and measured by some common yardstick; hence the very idea that we can weigh these kinds of costs against these kinds of benefits is an illusion;
- cost-benefit analysis cannot, it is claimed, be appropriately applied to situations where one party – the research animal – can only ever lose, and never gain: "Cost/benefit analysis fails to recognise that benefits accrue to one group whilst the costs are borne by others" (Anon.; so also e.g. University of Sheffield). The concern is that such an application is in breach of justice. If it were applied between humans, the practice would never be agreed to in advance by people unaware of which role they would occupy (Rawls' test of justice; cf. Rawls 1971);
- benefits and costs, it is claimed, are not morally neutral: values will already come into play in deciding what counts as a benefit (cost), which benefits (costs) are relevant, and so forth; as stated in the submission from The Royal Society: "what are presumed to be costs and benefits will themselves be heavily dependent on value systems";
- benefits and costs, it is claimed, cannot necessarily be identified independently of each other. Health, for example, is usually considered an unconditional benefit. But what counts as a benefit, and what counts as a cost, is crucially a matter of context. So it may be that health that is bought at the expense of animal suffering should not be judged a benefit;
- the criterion most widely used in cost-benefit analysis to determine whether or not benefits outweigh costs – the Hicks-Kaldor (or 'potential Pareto') criterion – cannot be applied to animal

experiments. This criterion says that benefits outweigh costs if those who gain can, in principle, compensate those who lose, and still be better off. Experimental animals, however, cannot even in principle be compensated in this way.

In addition to these difficulties of principle, certain determinations of cost-benefit appear particularly problematic. One notable example is how to reckon death – a question on which respondents were sharply divided; yet, as one respondent notes: "to include death as a discrete element in the equation has enormous consequences" (Anon.). A typical response ran as follows: "Views within this institution differ on whether death in itself should be considered a harm. Some would argue that, although causing death is not without its moral consequences, death is inevitable and the cost of shortening a life ... is very uncertain. Others would contend that death is definitely a cost, which must be subjected to the three Rs in the same way as for work on living animals" (Anon.). This last point was echoed in other responses, namely that the aims of reduction and replacement seem to imply that death is indeed to be reckoned as a cost. The question then becomes – how big and what kind of cost? The response quoted above points to an answer that might command some degree of consensus. The nature of the cost involved lies primarily in the shortening of life and the curtailing of benefit. It might therefore reasonably be considered greater in animals capable of a certain degree of anticipation, and in social animals who respond to the deaths of others of their kind. The chief source of uncertainty would seem to be those animals with lower capacities of anticipation and who do not 'count the number of their days'. But many would argue that their lives still have 'intrinsic' value, so that their deaths cannot count for nothing. Indeed, some respondents regarded death per se as "the ultimate harm" (Anon.), but this was not the view of the majority, who tended to view suffering as a greater harm than a humane death.

During the recent foot and mouth epidemic, there was a public outcry over the slaughter, even though the actual number of animals slaughtered was calculated to be less than would have been slaughtered during the 'normal' operation of the food chain. This strongly suggests that 'wasted' deaths are judged more harshly than deaths that are perceived to serve some purpose, and might reasonably therefore be judged to bear a heavier cost. Hence, perhaps, the comment that "it would... be absurd if the fact that some animals were likely to be killed as being surplus to requirement was not factored into the cost/benefit test" (BUAV).

Another difficult issue is the status of harms that involve no suffering. At least one respondent is extremely perplexed by the fact that procedures leading to death should be 'unclassified' with respect to harm i.e. they are perceived as carrying no 'cost' (Anon.). It might be useful here to distinguish between two kinds of case. On the one hand, invasive procedures carried out under terminal anaesthetic do not appear to add an additional cost to whatever cost is already assigned for the shortening of life. On the other hand, invasive procedures which an animal is allowed to survive and which leave the animal seriously unable to cope, even though with little awareness of its condition, must surely be judged more critically. The case appears to demonstrate a flaw in the exclusive focus upon suffering in the assigning of costs; not all harms need involve suffering. (See further Ch. 4: 4.4–4.5.5)

On the other side, there is some support for the view that the case for animal experiments can be made fairly decisively on the basis of consequential type arguments. These include the argument from vital needs, and the argument from necessity.

The argument from vital needs (i.e. needs for which provision is directly necessary for the continuance of life) is commonplace. We are invited to consider which is more important, the life of a dog, or the

life of a child. The thought is that where vital needs are in question, we can – and indeed ought – to put a human life first. Despite its popularity however, this style of argument is more problematic than it seems at first sight. For the fact is that we regularly countenance institutions and practices that put vital human needs at risk, even though they serve less than vital human needs. Examples include the various forms of transport, and also numerous leisure activities – swimming, sailing, climbing and the like. If, then, we routinely allow less than vital human needs to trump vital ones, we must ask ourselves why we are entitled to make an exception in the case of animal research. If we judge that invasion of animals' vital needs is justified to serve vital human needs, when we are unwilling to temper less than vital human needs for the same purpose, we are judging less than vital human needs more urgent than vital animal needs. And that judgement is more problematic. Another, simpler, point, is that in animal research we are rarely, if ever, presented with the stark situation in which we can save the life of a child by taking the life of an animal. Invariably, other choices and options intervene. Hence, it is perfectly coherent to oppose animal experiments, by arguing that other options and choices are possible, but save the child if we are faced by the stark choice.

This point connects to the second argument – the argument from necessity. The argument from necessity (see e.g. Smith and Boyd 1991, p.37) suggests that an action is justified if:

i) the evil prevented is greater than the evil done, and
ii) there is no less drastic method of achieving the stated aim.

Examples offered of such justified action include the killing of a hijacker to save other passengers, and surgical intervention to avert a life-threatening disease. Since both conditions are applicable to at least some animal experiments, it is argued, then they too are justified. However, the argument appears to have a flaw. In both the examples cited, a third condition is also present – namely that the lesser evil (or equivalent) would have happened anyway. But this is not true in the case of animal experiments – it is not true that the animals would suffer anyway. The decision to experiment on animals is not in the same way a 'forced' decision. Hence the justification does not carry over to the disputed case. The argument from necessity, then, does not demonstrate that experiments on animals are justified, though of course it is open to their defenders to propose other arguments.

The issue of necessity opens up areas of legitimate disagreement. But it also opens up areas for possible negotiated compromise. If there is a weakness in the case for animal experimentation within the terms laid down by the Act, it lies in the difficulty of demonstrating necessity. The challenge, indeed the requirement of the Act, is to demonstrate in any given case that there is no alternative to animal experimentation of the kind proposed – that the desired and desirable objective cannot be achieved in any other way. If this were interpreted as the requirement to show that the desired result could not be achieved in any other way, then it would be very difficult indeed to demonstrate. In principle, and with enough changes assumed, any number of desirable results *might* be achieved. It is usually, and more plausibly however, interpreted as a requirement to show that the desired result *is not likely* to be achieved in any other way. But this means – 'is not likely, given present circumstances'. It is therefore open to opponents of experimentation to argue that present circumstances should be changed so as to make it more likely. Herein lie the openings for compromise and negotiated targets that, in Chapters 4 and 5, we suggest should be pursued.

2.5 Conclusion

In this Chapter we have indicated some important common ground upon which the Act is premised.

This lies chiefly in the widely shared belief that animal suffering cannot be viewed as a matter of moral indifference, and that critical evaluation and justification is called for. This fact also helps explain the character and structure of the Act, especially the important element of cost-benefit assessment, and the role of this assessment in fostering the appropriate sensitivities. In reflecting on the arguments for and against animal experimentation, we have found there to be morally defensible considerations adduced for a range of views. However, we have also detected ways of keeping up the momentum for change, both by distinguishing more sharply between arguments that deserve to be ignored and arguments that cannot be ignored, and by identifying areas of potential compromise and negotiation.

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CHAPTER 3

THE SCIENTIFIC VALIDITY OF ANIMAL EXPERIMENTS

3.1 Introduction

The Animals (Scientific Procedures) Act 1986 requires that cost-benefit assessments, including assessments of scientific validity, be made case-by-case. These cost-benefit assessments operate on the assumption that animal experiments *can*, at least potentially, be scientifically valid and that benefits can result. Some anti-vivisectionist positions challenge this assumption absolutely. If such categorical denials of scientific validity are accepted, the Act, and with it the cost-benefit assessment, becomes redundant, since *no* animal experiments can be justified. This Chapter examines claims concerning the scientific validity of animal experiments and comes to the conclusion that scientific validity cannot be argued in absolute terms.

At one extreme, an absolute, categorical position that all animal experiments are scientifically invalid is untenable. However, so too is the opposite categorical position, that the validity of using animals in experiments is a forgone conclusion and should not be questioned. The case that animal experiments can produce scientifically valid results is clear, strong and sustainable, but cannot be construed as an absolute case that every potential use of animals is scientifically valid and fail safe. Nor, moreover, does the case that valid extrapolations can be made from animal experiments necessarily imply that the use of animals is the only or best means of achieving the particular objectives.

Scientific validity is a necessary, but not a sufficient, condition for animal experiments to be judged acceptable according to the cost-benefit assessment required under the Act. It is a condition capable of being fulfilled, but has to be judged case-by-case and subjected to detailed, critical evaluation.

3.2 Background

If animal experiments are to be worthwhile and potentially beneficial, they must (like other scientific methods) be capable of giving results that are (i) relevant to their purpose and (ii) reliable, in that they are reproducible within and between laboratories and over time. If animal experiments are not, or as is sometimes claimed, can never be scientifically valid in these terms, the cost-benefit assessment becomes redundant, because there will be no potential benefits to weigh against the harms and the use of animals cannot be justified. Consideration of the scientific validity of using animals is therefore an essential precursor to cost-benefit assessment *per se*.

Home Office *Guidance on the Operation of the Animals (Scientific Procedures) Act 1986* (Home Office 2000) clearly states that scientific validity must be examined as part of the cost-benefit assessment of project licence applications required under Section 5(4) of the Act:

"In assessing likely benefit, the Secretary of State must be satisfied that the programme [of work] is scientifically valid and likely to meet the stated objectives" (para. 5.12).

This will involve asking practical, scientific questions about the choice and design of animal studies, in order to determine whether and how far the proposed use of animals is reliable and relevant to the objectives or questions being asked. More widely, it should also involve asking whether and how far the proposed use of animals is the most appropriate approach - including whether it is appropriate to use animals at all.

Since this Chapter is about the scientific validity of animal experiments, the focus here is on scientific questions and arguments. The issue also embraces questions about the contributions to biomedical understanding that the use of animals can make, including whether and how far the outcomes of animal experiments are valuable, useful and/or communicated. These are explored in Chapter 4 of this report. Responsibilities for assessing scientific validity are considered in Chapter 5, on practical procedures for cost-benefit assessment.

In this Chapter, we:

(i) examine whether the scientific validity of experiments on animals can be argued in categorical terms or whether it can only be considered case-by-case;
(ii) describe factors that should be taken into account in assessing the scientific validity of using animals; and
(iii) explore some questions and concerns about the assessment of the scientific validity of projects and individual experiments under the terms of the Act.

3.3 Arguments concerning the scientific validity of animal experiments

Box 1 summarises the main general points typically made in categorical, anti-vivisectionist arguments that it is *not* scientifically valid to use animals in research and testing.

Such criticisms are mainly levelled at studies in which the intention is to extrapolate the results to humans - that is, the use of animals in:

- medical and biological research, in which:
    a) it is intended that findings from animal studies will be applied in clinical practice (comprising 26% of laboratory animal use in Britain in 2001), and/or
    b) animal studies are carried out "with a view to providing a practical solution to a medical problem once the issues are more clearly defined and understood" (detailed statistic not available, since data on this use of animals are combined with similar veterinary studies and work aimed "solely at an increase in knowledge" – Home Office 2002, see also para. 3.4 below); and
- toxicity and efficacy testing, where the aim is to assess the toxicity and efficacy of pharmaceuticals as a prelude to clinical trials, or to assess the hazards posed by other chemical substances to which humans are exposed (*circa* 15% of laboratory animal use in Britain in 2001).

The key contention is that that there are "crucial differences... from the cellular level upwards" between humans and other animals, which "result in misleading information from animal experiments" (National Anti-vivisection Society, NAVS). For this reason, it is argued that "it is hard to imagine any exceptions to the absolute position that animal experiments are not valid in terms of application to human medicine, toxicology, or pharmacology..." (Animal Aid). Moreover, the "similarities between humans and other animals are frequently overstated by pro-vivisection scientists and concentrate on superficial similarities" (NAVS).

In addition to these uses of animals as models of humans in experiments, smaller numbers are also used in work in which the research goals are better understanding of the animals themselves, or the acquisition of general biological knowledge. For example:

- applied veterinary research, which comprised around 7% of all laboratory animal use in Britain in 2001;
- zoological, botanical and ecological research, which comprised 0.9% of total animal use;
- animal welfare studies (0.05% of all use - some of which may overlap with the applied veterinary research category);

- toxicological studies aimed at assessing the effects of chemicals on the general environment (1.4% of all animal use), and
- fundamental biological research "aimed solely at an increase in knowledge" (detailed statistic not available, since as previously noted this category is combined with fundamental studies which are aimed at understanding the issues underlying medical and veterinary problems – Home Office 2002).

Critics apply the same argument about species differences to studies in which animals of one species, such as mice, are used to study clinical problems, basic physiology or toxicity in animals of a different species, such as horses. However, this species differences argument cannot be used in relation to work that is intended to provide insights that can be applied to other individuals of the same species - such as most zoological and ecological research, some veterinary research, and some toxicological and fundamental research. In such cases, the experiments are not opposed on scientific grounds, but on moral grounds, that it is fundamentally wrong to harm animals, whatever the likely benefits. See Chapter 2 for further discussion.

The main points typically made in arguments that express a case *for* the scientific validity of using animals in research and testing are also shown in Box 1, in which the positions 'for' and 'against' are contrasted. These arguments, though frequently strongly put, are not usually intended to be categorical: "the validity of animal experiments cannot be regarded as an all or nothing affair, although those totally opposed to research involving animals make the claim of no validity" (Anon.).

The case in support of scientific validity, like the case against, is usually made in relation to situations in which animals are used as models for humans, but would also be directly applicable in veterinary and other forms of research and testing. The key contention is that similarities between humans and other animals mean that "inferences" from animal models to other animals of the same or different species, including humans, "are possible but require care". "Animal models need to be very carefully selected and findings cross-checked... before extrapolation can be made with confidence, but it is important to recognise that such extrapolation is possible and valid" (Laboratory Animal Science Association of the UK, LASA). Further to this, it is also asserted that "indisputable evidence that animal studies often yield important and worthwhile new medical knowledge" supports "the use of animals as one of a range of valid research methods" (MRC). This is "not [to] claim that every experiment gives valid results... what matters is that each research programme should be rigorously scrutinised to ensure its validity".

Case study examples are employed in support of both of the general positions summarised in Box 1. However, examples are used in different ways by opponents and proponents of the scientific validity of using animals in research. Opponents tend to use specific examples to infer a general case, that the method as a whole is scientifically invalid. Proponents of scientific validity, on the other hand, tend to use examples to illustrate that the use of animals can be scientifically valid, and produce useful results, but not usually to argue an absolute case that every imaginable use of animals would be scientifically valid and capable of bringing worthwhile benefits. Rather, although proponents maintain that animal experiments can potentially bring benefits, they also assert that scientific validity has to be argued for, and considered critically, case-by-case. This is the position under the Act.

It was for this reason that the Annex to the consultation document (reproduced as Annex B to this report) only provided examples of claims made for scientific validity. The existence of invalid cases

Box 1: Main points typically advanced in general arguments 'for' and 'against' the scientific validity of animal experiments

AGAINST	FOR
Species differences meant that the results of most, if not all, animal experiments cannot be extrapolated to humans, or to other animals. For this reason, the results of animal experiments are not useful, and can be dangerously misleading. In the relatively few cases in which medical or veterinary benefits have resulted from animal experiments, the same results could have been achieved in other ways. The majority of animal experiments could be replaced with non-animal alternatives, including in vitro tests, humane volunteer studies and use of human tissues, which would produce more scientifically valid results.	Similarities between evolutionarily related animals (such as between humans and other mammals such as mice) makes extrapolation of results between species possible. For this reason, the results of animal extrapolation of results between species possible. For this reason, the results of animal experiments are useful. They have lead directly or indirectly, to numerous medical and veterinary benefits and have advanced fundamental biological knowledge, so as to provide a foundation for future benefits. Although non-animal methods are used wherever possible, it is difficult to mimic integrated physiological processes and behaviour in in vitro systems; there are ethical limits on human experiments; and supply of human tissue is difficult. Often using animals is the only means of achieving the objectives of experiments.

is not in dispute: it is the existence of valid cases that has been challenged, not the existence of invalid ones. Hence, contrary to the concern expressed by a number of anti-vivisectionist respondents (including the main societies), the aim of the Annex was precisely not to prejudge the issue of validity, but to present an opportunity for the opponents to make their case. In the event, whilst some respondents included examples of animal work that they judged scientifically invalid, there was no convincing attempt to challenge the particular examples presented in the Annex.
It should be noted, however, that the confrontational arena in which public debate about animal experiments takes place tends to encourage rhetoric that suggests categorical views on both of the 'sides' illustrated in Box 1. For example, although proponents of the scientific validity of using animals in experiments believe that validity has to be argued for case-by-case, their public statements can incline towards the absolute, in much the same vein as their opponents' statements: "Success in understanding and treating such diseases (e.g. heart failure, stroke, Alzheimer's, arthritis, diabetes, emphysema) will *inevitably* require the use of experimental animals" (UK Life Sciences Committee (UKLSC) web-site: www.lifesci.org). "The teratogenic effects of thalidomide would *certainly* be avoided today because of more extensive testing on animals" (UKLSC web-site).

More detailed, subtle arguments underlie both of the general positions illustrated in Box 1, and these have to be considered in drawing conclusions about the relative strengths of the competing claims.

3.4 More detailed analysis: the role of examples in debate about the scientific validity of animal experiments

As noted, those who oppose animal experiments tend to employ specific examples to support a general case that animal research is scientifically invalid. These examples are of at least five, interrelated, kinds:

1. Cases in which species differences mean that animals are not valid 'models' for humans, and in which it is asserted that experiments have failed because of species differences.
2. Examples in which animal experiments have failed to predict adverse human responses to medicines or other substances that have been marketed and widely used. High profile withdrawals from sale are often cited.
3. Examples in which it is argued that the use of animals was not the (most) appropriate approach, in that the same, or better, information could have been achieved in other ways, e.g. through use of *in vitro* tests, or clinical studies in humans.
4. More general examples of areas of research in which it is claimed that preventative medicine and public health measures have made a greater contribution to improvements in human health than drug or other 'scientific' medical interventions whose development involved the use of animals. For example, observations that major reductions in incidence of many common infectious diseases came with the introduction of clean water and good sanitation in the last century in Europe, before effective vaccination was available; arguments that possibilities for preventing cancers through environmental and/or life-style changes could remove the need for curative approaches.
5. Cases in which animal experiments are considered to have had no benefits, because the objectives were not original, not relevant to humans or other animals, not current, not worthwhile and/or because the experimental design was poor (see also Chapter 4).

See, for instance, BUAV, NAVS and Uncaged Campaigns web-sites for specific examples under each of these headings (www.buav.org; www.navs.org.uk; www.uncaged.co.uk).

To such examples is added the contention that,

6. The results of many animal experiments are never published, because the tests have failed.

The following responses can be made to the different kinds of example used in arguments that animal experiments are scientifically invalid:

3.4.1 Cases in which species differences mean that animals are not valid models for humans

Fundamental biological similarities, from genes upwards, between animals that are evolutionarily related, make it at least possible to extrapolate results from one species to another. Furthermore, analogues of many human diseases exist, or can be induced, in different species. Nevertheless, because there are also differences between species, animal models have to be carefully selected and the results of studies extrapolated with care and caution. Examples in which animal models for humans, or for other animals, have proved to be flawed strengthen the need for better understanding and more critical evaluation of their use, case-by-case. Moreover, understanding such differences can sometimes give clues about the causes of diseases and how they might be treated (Motor Neurone Disease Association response). For example, finding out why mice with muscular dystrophy suffer less muscle wasting disease than human patients could help in developing treatments.

3.4.2 Examples in which animal experiments have failed to predict adverse human responses to medicines

Before they can be marketed, all drugs are tested by non-animal methods and animal methods, and then in human clinical trials. This is a regulatory requirement. The animal studies are designed to show up serious side effects before tests are allowed to proceed in humans, and also to set dose levels, examine metabolism of the compounds and generate preliminary safety data. A side effect that shows up only after a drug has been marketed has not been revealed by *any* of the tests that are applied, including human clinical trials, which usually involve several thousand volunteers or patients. Moreover, since decisions to market medicines are based on the results of clinical trials,

such adverse responses reflect at least as much on the adequacy of the tests in humans, not animals. Note here that all drugs have at least some side effects. Some drugs are marketed even though they have serious side effects, because their benefits are seen to outweigh the adverse effects on the patients.

That serious side effects occasionally become apparent only after a drug is marketed and used by many thousands of people is not surprising. Probability dictates that there is always the possibility that rare effects will not be detected in relatively small-scale tests in animals and humans. The animal tests that are applied to candidate medicines help to weed out many that are likely to have undesirable side effects. On average only two or three out of every 10 000 potential drugs make it to clinical trials (Association of the British Pharmaceutical Industry (ABPI) web-site: www.abpi.org.uk), the others being rejected for a variety of reasons, including side effects.

Nevertheless, in considering the correlation between animal test results and human experience with new pharmaceuticals, it may be more meaningful to compare animal toxicity data with effects on humans in the clinical trials that take place before the new medicines are marketed, rather than with post-marketing data.

In fact, there have been very few systematic attempts to assess the correlation between toxic effects observed in animal tests of pharmaceuticals and those shown up in clinical trials. Such studies are problematic, largely because compounds that are shown to have significant toxicity in animals are unlikely to proceed to human studies.

Perhaps the most useful investigation to date is that reported by Olsen *et al*. (2000). This is a multinational pharmaceutical company survey to assess the concordance between animal and human studies of the toxicity of 150 compounds in a range of target organs. A retrospective analysis of data from the animal tests for each compound showed that, overall, 71% of the adverse effects found in human clinical trials were predicted in the preceding animal studies (but were clearly not severe enough to prevent the clinical trials going ahead). Of this total, tests in rodent species predicted 43% of toxic effects seen in human trials, while the non-rodent studies (dogs and primates) predicted 63% of the adverse effects.

Interestingly, the results of this review are sufficiently open to interpretation to have allowed their use as part of arguments both for and against the usefulness of animal toxicity tests of pharmaceuticals.

In support of the scientific validity of the animal tests, it can be pointed out that such tests showed an overall predictive value for humans of 71%, even in cases where the toxic signs in the animals were sufficiently uncertain/marginal to allow the compounds to progress to clinical trials. Moreover, it can be asserted, the analysis provides no information on whether animal tests that show up more substantial adverse effects are predictive of equivalent effects in humans, because clinical trials will not have been carried out in such cases.

On the other hand, these same data are also used by critics who emphasise that over a quarter of the toxic effects found in the clinical trials were not picked up by the animal tests, and that the rodent tests failed to predict more than 50% of the significant toxic effects in humans.

Whilst it is difficult both to gather and to interpret such data, it is clear that there is a need for more efforts to assess the value of animal toxicity tests in predicting effects in humans – particularly since the results of an animal test are almost invariably used as the benchmark against which the validity of an alternative, non-animal test is assessed. Examples of failures to detect human side effects of

pharmaceuticals once again emphasise the need constantly to strive to ensure that animal tests, like all other pre-marketing tests of drugs including human trials, are as scientifically valid and predictive as possible.

3.4.3 Examples in which it is argued that the use of animals was not the (most) appropriate approach

Non-animal methods frequently *are* used in research - indeed it is often said that as much as 90% of medical research funding goes to work that does not involve living animals. Many research projects in which animals are involved also employ *in vitro* and clinical approaches. However, at present it is not possible to mimic many integrated physiological and behavioural responses and diseases in *in vitro* systems that avoid the use of intact, living animals. Experiments on humans would be ideal in avoiding species differences, but society places ethical limits on the degree of risk of harm to which human subjects can be exposed.

Nevertheless, in spite of these difficulties, examples in which it is claimed that non-animal methods could and should have been used can raise challenging questions. Such as:

- how far the use of animals is actually determined by tradition or convenience;
- whether appropriate effort is always put into considering alternative approaches; and
- what would be possible if more resources (both time and money), and incentives (such as prestigious prizes) were put towards the development of alternatives, and the task approached with strong motivation, commitment and unconstrained imagination.

Again, such examples emphasise that, in assessing scientific validity, critical evaluation of the need to use animals is always required, along with exhaustive, on-going efforts to avoid using animals wherever possible.

3.4.4 Examples of areas of research in which it is claimed that preventative measures have made a greater contribution to improvements in human health than scientific medical interventions whose development involved the use of animals

Improvements in public health can, and have, played a major role in preventing transmission and reducing the incidence of many infectious diseases, world-wide. But in many cases, eradication has been achieved only with the development of effective vaccines and methods of treating the diseases, such as antibiotics, which has involved the use of animals. Preventative medicine, including alterations in life-style and environmental factors, are all vital components of efforts to combat disease and improve human health, but 'interventionist' medicine is also vital. For example, although some cancers can be prevented through changes in human behaviour, others cannot, and, for these, effective treatments are still needed.

A general point in all such examples, however, is that although it is usually easy to show *correlation* between implementation of the various methods of controlling disease, whose development involved the use of animals, and improvements in human health, it is not always straightforward to prove *causation*. There is always likely to be at least some (healthy!) debate about the relative contributions of preventative and interventionist medicine in health improvements in the past, and in determining priorities for the future. The debate is reflected in the pages of the medical press, as well as in discussions about the value of animal experiments. Nevertheless, the example shows the importance of critically evaluating approaches to medical and scientific problems and asking whether and how far it is possible to avoid the use of animals by pursuing different strategies, such as preventative approaches.

3.4.5 Cases in which animal experiments are considered to have had no benefits, because the objectives were not original, not relevant to humans or other animals, not current, not worthwhile and/or because the experimental design was poor

There is no excuse for poor experimental design. The quality of experimental design is a key factor in the assessment of scientific validity - see 3.5 below for further discussion.

Otherwise, the issues of 'benefit' raised above widen the notion of scientific validity expressed at the beginning of this Chapter (para. 3.2) and are taken up in the following Chapter. For now, it can be said that there is no doubt that there have been benefits from animal experiments in the past, and that there is the possibility that future experiments can have benefits - but that neither of these general points implies that the benefits of proposed experiments should go unquestioned.

Assessing the scientific validity of proposed animal experiments in terms of the probability that they will bring worthwhile benefits is possibly the most difficult and contentious part of the cost-benefit assessment. People's perceptions of what counts as a 'worthwhile' benefit vary. There is disagreement about who has the expertise to make such judgements, who can be trusted to do so, and whether there is sufficient transparency in the process at present. Approaches to the assessment of benefit, as well as costs to animals, and the issues raised, are considered in Chapters 4 and 5.

3.4.6 The contention that many animal experiments are never published, because they have failed

Again, failure through poor experimental design or an inappropriate scientific approach means that animals' lives have been unnecessarily taken, and should not be excused. However, even when experiments are judged scientifically valid in these terms, they may still fail to give the hoped-for results. To a certain extent, at least, this is a feature of scientific endeavour, and it is not surprising that many experiments 'fail'. "It is inevitable that original research using animals or non-animal methods involves wrong turns and dead ends" (MRC). Nevertheless, there must also be the reasonable expectation that particular animal experiments will have worthwhile outcomes, and so, once again, there is a need rigorously to assess validity case-by-case. A related point is that, whilst negative results can be useful in determining future experiments, to be beneficial they must be communicated, so that others working in the field know where the wrong turns and dead ends lie - see Chapter 5 for discussion concerning publication.

In order to make their case, those who deny absolutely the scientific validity of using animals in research need to do more than demonstrate the existence of invalid uses. The citing of cases where animal models have proved misleading does not itself show that the approach is in principle misconceived. To argue that "because animal research has sometimes given misleading results, it is never valid" is "comparable to saying that because cancer chemotherapy does not always help, it should never be used" (MRC). What needs to be shown, in addition, is that the reason, or reasons, why animal models prove misleading in particular cases in fact apply across the board – that is, that the cases of failure are symptomatic of some general flaw. Moreover, to show this, it is not enough to appeal to the differences between species, even though these are crucial from various points of view. What matters is whether these differences are relevant to the basis of the extrapolation that is being made. The existence of differences is perfectly compatible with the existence of similarities - of which, as we would expect from our recent common evolutionary origins, there is a whole array, between mammalian species especially. What is at issue here, as far as concerns scientific validity, is whether these similarities can form the basis of reasonable

extrapolations – in effect, whether they can generate significant probabilities. No inductive model should be expected to be 100% accurate, and in an empirically based science there will always be a gap between a model and what it models. The fact that one can show there is such a gap is not a demonstration that this is bad science, but a demonstration that it *is* science.

On the other hand, the fact that an extrapolation has proved successful in a given case (e.g. a drug proved effective in a particular strain of rodent also proving effective in the case of humans) is not, in itself, enough to validate the extrapolation. It is always possible that the result was somewhat 'lucky', and would not have been obtained if the research team had happened to use a different species or strain. Until this possibility has been ruled out, the validity of the extrapolation will be in question. But this circumstance is exactly in accord with what we should expect of an experimental method. It needs to be recognised, furthermore, that the notion that similarities are the only basis for useful extrapolations is unduly simplistic: "it is often the differences between species that provide the most valuable insights" (Motorneurone Disease Association).

3.4.7 Conclusions

Those who deny the scientific validity of animal experiments tend to use specific examples that they consider scientifically invalid to infer a general case that all animal experiments are invalid - whereas proponents tend to use examples to illustrate that animal experiments are typically scientifically valid, but maintain that every case has to be considered on its own merits. Those who put the case for scientific validity contest the facts of some, but not all, of the particular examples used by those who espouse a case against validity.

Where they are accurate, examples of scientifically dubious or invalid animal experiments lend weight to the need to critically evaluate scientific validity case-by-case and highlight that the evaluation is not always critical enough. But they do not add up to a general proof that animal experimentation as a whole is flawed science. To show that the science as a whole is flawed, it would need to be shown that the cases of failure are indicative of some general flaw. And this, in our view, has not been shown.

It is incorrect to assert that differences between species mean that it is rarely, if ever, possible to extrapolate the results of experiments from animals to humans, or from one animal species to another. There are fundamental biological similarities between all living beings, particularly but not exclusively those that are closely evolutionarily related, that make it at least possible to extrapolate results from one species to another, provided the model species are carefully chosen. Indeed, fruitful extrapolation is sometimes possible even between species that are evolutionarily very distantly related. For example, important advances in understanding of human genetics have come from studies on yeast and nematode worms. Moreover, there are myriad examples in which animal experiments have advanced biological understanding in a wide range of disciplines, and in which such knowledge has helped to bring benefits to medical and veterinary practice. **An absolute position that *all* animal experiments are scientifically invalid is therefore untenable.**

Nevertheless, an opposite absolute position, that the validity of using animals in experiments is a forgone conclusion and should not be questioned, is equally untenable. The case that animal experiments have been, and can be, scientifically valid is clear, strong and sustainable, but cannot be construed as an absolute case that every potential use of animals is scientifically valid.

Scientific validity is a necessary, but not a sufficient, condition for animal experiments to

be judged acceptable according to the cost-benefit assessment required under the Act. It is a condition capable of being fulfilled, but has to be judged case-by-case and subjected to detailed, critical evaluation.

This is the view taken by all respondents to the APC consultation who do not hold a categorical anti-vivisectionist position, including researchers, animal welfare organisations and others. For these respondents, the key question with respect to validity is not *whether* animal experiments can be scientifically valid, but *how* scientific validity can best be critically evaluated and ensured. Indeed, most responses, including those from the main anti-vivisection groups, concentrate on this aspect, and many respondents offer observations and ideas that they consider can help to strengthen the assessment of scientific validity, case-by-case.

The above remarks apply specifically to the issue of scientific validity, so far as it concerns the reasonableness of the animal model. It is important to remain aware of what validity in this sense does, and does not, imply for the issue of validity in a wider sense. In particular, to show that it is often valid to use animal models as a basis for extrapolation does not imply that this is the *only* way of achieving the information that is sought, nor in general, the only way of advancing biomedical research. Nor does it necessarily follow that this is the best way of achieving the information or, in general, the best way of advancing biomedical research.

Finally, it is worth remarking that existing regulations already incorporate some compromises over scientific validity due to ethical concerns. Most obviously, a wide variety of experiments on humans are forbidden, even though these would generally produce the most valid results.

3.5 Criteria for assessing the scientific validity of animal experiments

The criteria set out in paragraph 8 of the consultation document (Annex A) appear to provide an acceptable general framework for assessing validity, with the exception of the last point - the benefit of fortuitous discovery - which a number of respondents feel is an unacceptable reason for using animals (see Ch. 4: 4.5.6 for further discussion). It is clear, however, that these broad factors need to be amplified. Many of the responses suggest additional or expanded criteria, and some provide examples of assessment schemes, which are used in a variety of contexts.

Box 2 summarises the various criteria suggested in responses and also draws on published schemes that are intended to provide guidance on cost-benefit assessment of animal experiments, and which include guidance on assessment of scientific validity. These include schemes produced by:

- Delpire *et al*. (1999) - a scheme intended for use throughout the EU, appended in Professor Michael Balls' response; relevant parts of which are also reproduced in NAVS's response, as a list of criteria for assessing validity; and
- the MRC - a list of *Assessment factors for referees*, submitted with the response.

Many of the points in Box 2 are similar to those listed in Home Office guidance (notes from the Chief Inspector, 1993 and 1997 (Home Office 1998); *Guidance on the operation of the Animals (Scientific Procedures) Act 1986* (Home Office 2000); and notes to applicants for project licences (Home Office 2001a). We have collated key questions from this published guidance, in order to illustrate the Home Office Inspectorate's approach in assessing scientific validity. These are summarised in Box 3.

Although the factors listed in Boxes 2 and 3 are expressed rather differently, they cover much the same ground. Compared with the Home Office guidance (Box 3), the collated criteria suggested in responses to the consultation (Box 2) tend to be more elaborate and detailed, particularly concerning

the validity of the choice of animal methods, and factors relating to where the research is carried out and by whom.

Box 3 is a best attempt to summarise the guidance on assessing scientific validity published by the Home Office, which is spread over several different documents, each of which has been produced for a different purpose. Within these documents, the factors relating to scientific validity have to be extracted from a variety of sections and disentangled from other factors that are important in the cost-benefit assessment. The notes to applicants for project licences (Home Office 2001b) offer the most comprehensive advice, but are not particularly user-friendly.

Box 2: Summary of criteria for assessing validity suggested by respondents, and in published assessment schemes

1 Validity of the scientific approach to the particular question or problem

1.1 Validity of using animals *at all*

- Are there compelling reasons for believing that using animals will give insight into the particular question or problem?
- Has the possibility of using other, non-animal, approaches been rigorously explored? What sources / authorities have been consulted, what information has been obtained and how has it been evaluated?
- Are any other approaches, such as in vitro or human studies, feasible? If so, would they be equally or more likely to achieve the desired results?

1.2 Validity of the choice of animal method(s)

- Is there a sound scientific basis for believing that the animal methods are relevant to the experimental objectives?
- Have the animal methods previously been validated, or otherwise shown to give results that can be extrapolated to the particular circumstances in which a benefit is sought (e.g. to humans, or another species, to the particular age group, disease state, level of chemical exposure involved)?
- Are the relevant similarities and differences between the animal model(s) and the species in which the benefit is sought clearly understood, and can the limitations of the model(s) be overcome?
- If novel methods are proposed, have any pilot studies been carried out, and if so, what were the results? If not, how will the validity of the animal methods be evaluated?
- Are there any existing experimental data, or other experience, to suggest that selection of different species and/or method(s) would render the conclusions of the project more generally relevant or allow you to obtain more useful information?

Is any refinement of the approach possible, so as to reduce suffering caused to the animals?[1]

1.3 Validity of the experimental design

- Are the specific aims and objectives of the experiments clearly defined, and are the working hypotheses clearly defined and testable?
- Are the objectives realistic within the timeframe and with the resources proposed? (See also 1.4 below)
- Has the quality of the experimental design, including statistical aspects (such as group sizes, use of controls, proposed analyses) been demonstrated? What expertise has been employed in designing the studies, e.g. expert statistical input?
- Is the design appropriate to meet the objectives and/or test the hypotheses?

1.4 Other issues affecting the validity of the scientific approach

- Is the research team sufficiently multidisciplinary to ensure availability of all the competencies required to safeguard the quality of the work and achieve the objectives?
- Are all workers sufficiently trained and experienced in the proposed approach? If not, what training will be undertaken and/or how will experience be gained?
- Is there consultation / collaboration with others working in the field, to ensure that the procedures are optimised and unnecessary duplication / replication of work avoided?
- Are all the necessary facilities for carrying out the experiments and caring for the animals available and of a standard that will safeguard the quality of the work?
- Is adequate, secured, funding available to achieve the objectives of the work within the time-scale proposed?

Box 2 continued: Summary of criteria for assessing validity suggested by respondents, and in published assessment schemes

- Is the time commitment of the researchers to the project appropriate and sufficient to meet the aims of the work?
- What is the track record of the researchers? Have the aims and objectives of any previous projects in this field been met? What have been the benefits of any research carried out by the team to date?
- Is the "environment" appropriate for the proposed research?[2]

2 Contribution to knowledge (etc) that the animal experiments are likely to make

- This widens the interpretation of scientific validity to embrace questions about the likely scientific benefits of the studies, including whether and how far the outcomes of animal experiments are valuable, useful and/or communicated. Specific criteria are elaborated in Box 3 and paragraph 4.4 in Chapter 4.

Notes:

1 This point clearly overlaps with assessment of 'costs' to animals. It will cover factors such as choice of species, choice of scientific techniques, housing, husbandry and transport of animals, end-points for the experiments, methods of monitoring animals and alleviating pain and distress, and method of killing or other fate of the animals (see Chapter 4). It is also included here because it is an important factor in choice of method, and may sometimes have to be weighed against potential effects on the science involved.

2 "Environment" is one of the assessment factors for referees of proposals submitted to the MRC. The specific questions asked under this heading are: Is the environment appropriate for the research proposed? Are the collaborators well chosen? Has the host institution demonstrated a clear commitment to the research programme proposed? Does the environment provide adequate opportunities for training and career development? Although not mentioned specifically by any of the respondents, or in any of the schemes, perhaps this might be equated with frequently used phrase "culture of care".

Box 3: Summary of questions asked by the Home Office in assessing scientific validity (collated from the sources listed in 5.3 above)

1 Likelihood of success (cf. validity of approach in Box 2)

(i) Has a sustainable scientific case been made for the use of animals?

- Is animal use necessary *at all* ?
- Has adequate, active consideration been given to the use of non-sentient alternatives?
- Is the choice of species justified, including special justification for use of non-human primates, dogs, cats, equidae, endangered species and animals taken from the wild?
- How were the proposed methods selected; what other methods were considered?
- Is an awareness of the scope and limitations of the animal models demonstrated?

(ii) Will the study design meet the stated objectives?

- Are each of the animal models and other research methods integrated into a coherent programme of work that will meet the objectives?
- What is to be examined, measured and recorded, and is it appropriate to meet the objectives specified?
- Are the proposed group sizes (numbers of animals) appropriate to the power or precision required in the experiments or bioassays?
- Is it demonstrated that sound, methods of appropriate statistical testing will be applied?
- Is provision made for any necessary pilot studies?
- Is specific, scientific and statistical justification made for the use of control groups, where necessary - especially the use of positive controls, non-treated controls to be exposed to microbiological agents and sham-operated groups?
- Is the use of control groups appropriate?
- Is suffering minimised whilst maximising information?
- What is the track record of the research group, its resources, training, facilities and published work?

2 Importance of objectives (cf. validity of contribution to knowledge in Box 2)

As in Box 2, this widens the concept of scientific validity to encompass questions about the likely value of the potential outcomes of the studies. Criteria addressed by the Home Office in this area are elaborated in Box 7 in Chapter 4, on assessment of benefit.

There would be merit in the production of an easy-to-use scheme for assessment of scientific validity (as well as for harms (costs) to animals and benefits - see Chapter 4), that could be used to guide researchers and others engaged in ethical review under the Act, such as members of Ethical Review Processes (ERPs). With this in mind, we recommend in Chapter 5 (5.4.1) that the Home Office should produce, or commission production of, a comprehensive list of factors that should be taken into account, perhaps as a guidance document that could be made available on the web.

3.6 Some further questions and concerns about the assessment of the scientific validity of projects and individual experiments under the terms of the Act

Ensuring the scientific validity of animal experiments is vital, and should be the first step in the cost-benefit assessment under the Act: "Scientific validity should be considered first, then only those projects that are valid subjected to cost-benefit analysis. An invalid experiment should not be carried out however little the cost in terms of animal welfare." (Physiological Society). In addition to the vital initial assessment, there also should be on-going assessment of validity throughout the life of a project, to "ensure that the research is carried out, and the results applied, in a valid way" (Royal Society for the Prevention of Cruelty to Animals, RSPCA).

Like other elements of the cost-benefit assessment, assessing scientific validity involves making judgements, based on detailed understanding of the objectives and design of the studies concerned. Clearly, it is in the nature of scientific experiments that the outcome is uncertain, and this means that *a priori* assessments of validity cannot be perfect or certain - rather they reflect a balance of probabilities. Not only this, but assessments of validity are likely to change over time, so that "as scientific knowledge grows and new analytical methods become available, it becomes possible to design experiments which are more informative and to use knowledge gained in new ways" (MRC).

Despite some polarisation in overall perspective, a wide range of respondents, whatever their general view on whether assessment of validity is currently adequate, offer questions and concerns. Notably, both opponents and proponents of the scientific validity of using animals raise similar issues, though opinions on them often differ.

3.6.1 Expertise, trust, openness and transparency

The main concerns relate to issues of transparency and openness in the assessment, and especially who has the necessary expertise and can be trusted to make informed judgements about the scientific validity of animal experiments. These aspects are considered in Chapter 5.

3.6.2 Role of factors such as tradition and convenience in determining scientific approaches

Some features of validity are easier to assess objectively than others. For example, assessing the validity of experimental design is relatively straightforward compared with assessing the validity of using animals at all or of the particular species/model proposed. The latter "might involve challenging the fundamental basis of a field of research that has traditionally been based on a particular animal model, but where an alternative approach might yield equally, or more, useful results" (RSPCA).

Of course, critical assessment, taking into account precedent and experience might show that the use of an animal model gives valid results and, scientifically, is the most appropriate method of achieving the object of the experiments. There could also be a need for comparability of new data with data obtained in previous experiments, which will limit how far approaches can be changed during a long-term series of experiments. But there are also criticisms that "scientific 'tradition' plays far too great a role in determining the approach ...and

research methods employed" (RSPCA). Similarly, critics also assert that 'convenience', rather than strict scientific validity and necessity can determine approaches.

In some circumstances, there can be obstacles to innovation in choice of scientific approach, as well as in framing the research questions in the first place. For example, the very availability of a particular animal model might determine the nature of the questions that are asked. Personal factors can also play a part, in that research careers may be built on the use of particular models, and it can be difficult to change when there has been a great investment of time and energy into a particular approach.

Time plays a role in this too. If using a readily available animal model can bring results more quickly than developing and validating a different model that might offer advantages or an alternative non-animal approach, this might be a legitimate factor in assessing the validity of the approach. This would also depend on the nature and significance of the likely outcome of the work, as well as the depth of consideration given to finding and developing an alternative. Speed would be of the essence, for example, if there were to be a need for rapid development of new vaccines in the case of re-emergence of smallpox.

Different research groups may use different animal 'models' to study the same problem. There can be sound scientific reasons for this, in that each model is useful in investigating different aspects of the problem - or, alternatively, the choice of model might be determined by tradition and convenience, rather than on strict assessment of validity. For example: "Several animal models are used to study human HIV (i.e. cats/ feline HIV, monkeys/simian HIV, chimpanzees/human HIV - the last abroad; the use of Great Apes is not allowed in Britain). Each is said to be a 'good model' of human AIDS, but do they all represent a 'valid' approach?" In deciding whether and how far all three are scientifically valid, a number of questions would be have to be asked, including, "Why are all three models considered necessary; what is each model used for; do they each provide useful information; is there sharing of information between groups; is the knowledge from each group consolidated and applied?" (questions in RSPCA response).

Individuals and establishments should consider whether and how far they always engage in sufficient innovative, creative, flexible and challenging thinking when choosing methods and models to address scientific research or testing questions, and how they might ensure that the choices are based on the kinds of factors listed in Boxes 2 and 3. This kind of critical questioning is a vital part of cost-benefit assessment more generally, and is particularly important in helping to avoid inertia in the application of the ethical framework of the Act. Note that these issues also raise questions about who has the expertise to judge scientific validity (see Chapter 5 for discussion), and particular questions about regulatory testing which are considered in 3.6.4 below.

3.6.3 Experimental design and statistical expertise

Valid experimental design is vital in ensuring the scientific validity of animal experiments, and, as a consequence optimising the use of animals, so that the minimum number possible is used to gain scientifically meaningful and valid results (see also Chapter 4, re reducing costs to animals). However, surveys of published papers sometimes have revealed basic errors (e.g. McCance 1995, Festing *et al*. 2002). This, as the Chief Home Office Inspector points out, means that the mistakes "have escaped detection by funding bodies, authors and the editorial boards and are now in the public domain" and is a situation that "needs to be remedied" (Richmond 2000).

Licensee training is important, but Module 5[1] training for project licence holders cannot, and is not, "meant to instil a lifetime's expertise in study design and conduct". Perhaps it should be acknowledged that "some aspects of practical science, such as study design and information management, should be provided by specialist advisers, rather than having each research group try to develop and maintain its own expertise?" (Richmond 2000).

Licensees must be aware of the necessity for good experimental design and planning, such as choice of appropriate models and experimental methods. They must also be aware of the importance of statistical input in their experimental designs, understand what can be achieved with wise statistical consideration, and know where to go for advice. It is important to evaluate the success of the experimental design component of Module 5 in imparting these general skills and understanding. The education and training sub-committee of the APC are considering this matter further and will make appropriate recommendations.

In addition, we recommend that each establishment should ensure that a statistical service is available to its licensees – establishments might collaborate in providing such a service. This statistical expertise could also be available to the ERP, to provide advice where required on statistical aspects of applications and on-going work that is subjected to local ethical review. Some establishments already provide such a service.

3.6.4 Assessing scientific appropriateness in animal tests for regulatory purposes

In 2001, just over 17% of all laboratory animals used in Britain were involved in procedures carried out for the purposes of toxicology or other safety or efficacy evaluation. 86% of these procedures were carried out in order to comply with legislation or other regulations (Home Office 2002). National and international regulations, such as the UK Medicines Act, EU Dangerous Substances Directive, Pesticides Directive and Biocides Directive set out clear requirements for particular animal tests to be performed in assessing the safety and efficacy of certain classes of substance. In respect of such regulatory requirements for animal tests, there is a range of views on whether and how far appeals to the law and/or the (perceived) demands of regulators can, in themselves, meet the requirements for scientific validity, particularly in terms of the scientific appropriateness of the tests.

Two of the responses we received to our consultation were from regulators. The Health and Safety Executive provided a paper describing steps it has taken to implement the 3Rs, but also comments that, "from a regulatory toxicology perspective, we do not feel we have a role to play in informing this review". The Pesticides Safety Directorate (PSD) argues that "ultimately... it must be the responsibility of the regulator to ensure that the study is relevant to the needs of the regulatory process". However, the PSD also observes that: "The scientific validity of animal studies submitted to PSD in order to comply with the legislation can be argued in absolute terms.... Pesticide legislation clearly sets out the programme of studies required to gain approval in the UK and EU and also makes clear the purpose and use of the testing involved. The range and design of standard studies have been carefully selected to cover the likely spectrum of toxicity, with non-animal alternatives introduced where possible. Theoretically, therefore, unnecessary and inappropriate testing should not be performed. The studies must be conducted under national/international guidelines, and the

[1] Module 5 of the education and training requirements for licensees covers ethical aspects of animal use, techniques for literature review and analysis, alternatives (the 3Rs), project design, project licence management and legal aspects of animal use. All modules are reproduced in the guidance on the Act (Home Office 2000).

justification for using particular animals is therefore well understood".

Companies, clients, individual scientists *and* regulators all bear responsibility for ensuring that only the most scientifically appropriate studies are carried out. Under the Act, ultimate responsibility for questioning and ensuring the scientific appropriateness of the use of animals in regulatory tests lies with the scientists conducting the work. Home Office *Guidance on the conduct of regulatory toxicology and safety evaluation studies* (Home Office 2001b) shows that a regulatory requirement is not, in itself, sufficient to justify particular animal tests. Project licence applicants must also "satisfy the Home Office on four essential requirements, that:

- there are no validated alternatives to the tests;
- animal testing will only be performed when there is reasonable, sustained justification for the new data;
- the protocols proposed cannot be further refined;
- the protocols will be likely to produce data that meet the specified objective".

And, moreover, they should not "over test" or adopt "check-list" approaches.

Although the regulatory process appears very specific, all regulatory authorities should be open to discussion and there should be opportunity to question regulations, so as to help avoid 'check-list' or 'tick-box' approaches in testing. This should ensure that only those tests that toxicologists consider scientifically appropriate are carried out, and allow for full application of the Three Rs. However, in practice it can be difficult to depart from the specific tests and approaches laid out in the regulations, especially since there are risks that data from the revised tests may later prove unacceptable to the regulators and so delay approval to market a new chemical ingredient or product, and/or render the company liable in the event of the new substance causing unforeseen adverse effects when manufactured, marketed and used.

International regulatory authority guidelines vary between countries, do not always keep pace with developments in toxicological understanding and thinking, and can be slow to adopt validated alternatives that better implement the Three Rs. There is considerable inertia in the system for approval of changes to the regulations, even where the revised tests have been subject to widespread scientific validation, and the current EU and OECD systems are considered by many to be unnecessarily cumbersome. There is scope for a more proactive process aimed at revising regulations to ensure that only the most scientifically appropriate tests are required, to remove check-list approaches and expedite acceptance of validated alternatives.

Although the Home Office and those who use animals under the Act can play a significant role in addressing this problem, they are not responsible for it. A range of different bodies share responsibility for resolving these issues, and need to make concerted efforts to achieve change. The International Conference on Harmonisation is an example of one such initiative. It aims to eliminate needs for repeat testing of human and veterinary pharmaceuticals to meet the requirements of different national and pan-national regulatory authorities so that the products can be licensed in different parts of the world. The work of the Conference involves addressing the scientific need for all the different parts of the testing process, and, as part of this, considering possibilities for incorporating more *in vitro* tests and reduction and refinement of animal tests into the process.

In this context too, the Home Office reports that it operates on a number of fronts (involving Ministers, the Animal Procedures and Coroners' Unit, and the Inspectorate) to try to progress change in regulatory guidelines. For example:

- actively liasing with other government departments and regulators in developing and interpreting regulatory requirements;
- consulting with and advising other government departments when national or international issues within their sphere of influence impact on issues within the Act (e.g. in determining the UK input in to the European Chemicals Strategy);
- maintaining a liaison group and concordat with UK regulatory authorities - and through them having influence when they meet with overseas regulators;
- representation on the UK OECD Shadow Group, and other UK groups involved with the European Chemicals Strategy;
- representing the UK on animal protection issues within CEN (the European standards agency) and ISO (the International Standards Organisation);
- participating in many international meetings putting the UK point of view and challenging attitudes and practices that prevail elsewhere;
- meeting national and international regulatory agencies formally and informally in the course of other business, and informal contact with international organisations such as OECD, EPA, USDA, FDA etc.

We conclude that there is an element of circularity in arguments about where responsibility for the scientific appropriateness of animal tests carried out for regulatory purposes actually lies, which is difficult to break. As noted above, although regulatory authorities should be open to negotiation so that only the most scientifically appropriate and necessary tests are carried out, it is not easy to challenge the requirements laid out in the regulations. Regulatory authorities do have a role in cost-benefit assessment of animal procedures, and need to allow scientists flexibility of approach to ensure that only the most valid and vital animal tests are carried out. By the same token, toxicologists for their part have a duty to continue critically to evaluate the appropriateness of the animal tests they perform and to raise questions and concerns with the regulators.

3.7 General conclusions

In this Chapter we have concluded that neither the case 'for' nor the case 'against' the scientific validity of animal experiments can be argued in absolute terms.

We have argued that scientific validity is a necessary, but not a sufficient, condition for animal experiments to be judged acceptable according to the cost-benefit assessment required under the Act. It is a condition capable of being fulfilled, but has to be judged case-by-case and subjected to detailed, critical evaluation.

To assist in this critical evaluation, we have collated lists of factors to be taken into account in the assessment of scientific validity, based on criteria mentioned in responses to our consultation and Home Office guidance. We observe that there would be merit in the production of an easy-to-use scheme for the assessment of scientific validity, and we make a recommendation in this regard in Chapter 5.

We note that prospective assessments of scientific validity are judgements that can change over time as scientific knowledge and techniques develop. In view of this, we have explored a variety of questions and concerns raised in relation to such assessments and, as part of this, have emphasised the importance of high quality statistical input in the design and analysis of animal experiments, as well the need for a suitably challenging and critical approach in the assessment of validity. Further issues relating to procedures for assessing scientific validity are explored in Chapter 5.

An experiment that is not capable of giving scientifically valid results should not be carried out – no matter how small the cost in terms of harm to

animals. Assessment of scientific validity is thus an essential precursor to cost-benefit assessment *per se*, which we begin to examine in the next Chapter.

3.8 References

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CHAPTER 4

THE IDENTIFICATION AND ASSESSMENT OF COSTS AND BENEFITS

4.1 Introduction

It is clear from the responses to our consultation that there is a range of opinion on what might be acceptable and unacceptable reasons for using animals in science, which species might be used and what procedures these animals might and might not be subjected to. Indeed, opinions differ not only on what should count as legitimate benefits and harms under the Act, but also on the relative weights that should be accorded to the different kinds of potential benefits and harms in the cost-benefit assessment. This is because assessments of both costs to animals and benefits are matters of judgement, which, by their nature, are contestable.

For example, in evaluating benefits, the values placed on different kinds of benefits will depend on the perspectives from which questions are asked. People suffering from a disease or condition may place a different value on animal research into that condition if they believe animal experiments have benefit, compared with people not directly affected; different people are likely to place different values on the use of animals to develop and test different products, depending on whether they use or benefit from the products concerned. As the RSPCA comments:

"The crucial decision regarding whether a benefit is sufficiently desirable (and necessary) to justify animal suffering and/or loss of life is difficult to make and clearly depends upon the individual opinions of those charged with making such decisions. Most people, even within the scientific community will have areas of research where they consider the potential benefits unjustified".

Similarly, although costs to animals can be more directly observed, and evaluation of their significance should be informed by detailed knowledge of the physiology, behaviour and life-style of the species, strain and individual animal concerned, judgements are still involved. At present, our ability to determine the relative pain, distress or other suffering experienced by animals of different species, undergoing different scientific procedures, is limited. As research data are obtained in this area, judgements about the relative costs of different procedures may change. Moreover, given the same information, different people will place different values on the various possible costs to animals, depending, in part at least, on their views on the moral status of the animals involved, the moral significance of harming animals, and the acceptability of animal experimentation in general.

Furthermore, the very nature of scientific endeavour means that the outcomes of projects, to some extent at least, are uncertain, otherwise there would be no point in carrying out the experiments. This implies that evaluation of benefits and harms can be based only on potential, likely and probable, not certain, outcomes. In addition, evaluation of potential and likely/probable costs and benefits is also likely to change over time, as understanding of animal welfare improves, scientific methods develop, and new knowledge becomes available. Moreover, the benefits of projects might not be fully realised until some considerable time after a given project is completed.

Because such contestable judgements are involved, it is important that:

(i) the *factors* taken into account in the assessment of costs to animals and benefits are widely known and agreed; and

(ii) the practical *process* by which the costs and benefits are evaluated and weighed one

against the other in any given case is as open and transparent as possible.

In this Chapter, we examine the costs and benefits that should be taken into account in a comprehensive ethical review of the kind required under Section 5(4) of the Act. In particular, we:

(i) examine the factors that are, and should be, taken into account in cost-benefit assessment - drawing together guidance that can assist the various mandatory and other review processes, including our own, to identify and assess all relevant costs to animals and scientific benefits;
(ii) comment on some areas that are perceived as problematic; and
(iii) ask whether some scientific uses of animals ought to be ruled out absolutely.

Practical procedures for cost-benefit assessment, including roles and responsibilities, needs for information and means of enhancing transparency, are considered in Chapter 5.

4.2 Information to assist in identifying harms and benefits

In the next two sections of this Chapter, we present criteria for the identification of costs to animals and benefits. The factors described in currently available Home Office guidance are drawn together, and are compared with criteria suggested in responses to our consultation and in other published schemes for assessment of costs and benefits.

4.2.1 Information on current Home Office practice

Three documents provide some insight into how Home Office inspectors currently apply the cost-benefit assessment. These are:

1. *Guidance on the operation of the Animals (Scientific Procedures) Act 1986* (Home Office 2000c), particularly Chapter 5, on Project Licences, and the brief description of cost-benefit assessment presented in Appendix I (Home Office 2000b);
2. *Chapter 2, in Appendix F to the Report of the Animal Procedures Committee for 1997*, which includes two annexes: (i) *The cost/benefit assessment: a note by the Chief Home Office Inspector* and (ii) *Assessment of benefit and severity: a 1993 note by the then Chief Home Office Inspector* (Home Office 1998a), which, taken together, provide a more detailed description, on which the summary in the Appendix I, referenced above, is based; and
3. *Notes to applicants for project licences under the Animals (Scientific Procedures) Act 1986* (Home Office 2001a), which describes the information that project licence applicants must supply to the Home Office in order to allow a cost-benefit assessment to be performed.

The assessment is usually carried out "at the level of the whole programme of work set out in the project licence application" (Home Office 2000a) and applicants are required to provide sufficient information and analysis to demonstrate that:

(i) the potential benefits of the project are "desirable, attainable, and clearly exceed the expected welfare cost";
(ii) benefits are maximised and costs in terms of animal use and suffering are minimised; and
(iii) reduction, refinement and replacement strategies (the 3Rs) are properly implemented (Home Office 1998a and 2000a).

It is apparent that a key consideration underpinning all of these factors is whether and how far project proposals can be considered to be scientifically valid and likely to meet their stated objectives. If a project has dubious scientific validity it should not be undertaken, no matter how small the cost to animals. We have considered issues relating to the scientific validity of animal experiments in Chapter

3 of this report, drawing the general conclusion that scientific validity is a condition capable of being fulfilled by projects involving animals, but has to be judged case-by-case and subjected to detailed, critical evaluation. Criteria for assessing scientific validity (including those described by the Home Office) are also explored in Chapter 3.

4.2.2 Other published guidance

A variety of schemes for ethical review of animal research and testing have been published. Some of these cover assessment of both benefits and harms, others relate to harms only. A selection of these schemes is listed in Annex D.

4.3 Factors in the assessment of costs to animals

The Home Office approach in assessing costs to animals is described in Boxes 4 and 5. The material has been collated from all three of the documents listed in 4.2.1. Box 4 describes the overall scope of the assessment and Box 5 lists the factors that are taken into account.

Box 4: Definition and scope of costs considered in assessment by the Home Office

1. Costs are defined as the adverse effects, i.e. pain, suffering, distress or lasting harm, likely to be experienced by the animals used during the course of a study.
2. This includes any material disturbance to the normal health, i.e. to the physical, mental and social well-being, of the animal, and covers disease, injury and physiological or psychological discomfort.
3. Both immediate effects, e.g. transient discomfort from injections, and longer-term effects, e.g. the subsequent toxic effects of test materials, are included.
4. Costs arising from both regulated scientific procedures and husbandry and care systems are considered, and all of the interventions applied to an animal or group of animals from the time they are issued from stock until they are killed or discharged from the controls of the Act are covered.
5. Regulation of scientific procedures starts at the level of adverse effect cause by "skilled insertion of a hypodermic needle", or equivalent, depending on the procedure. It is noted that the following procedures are covered:

- minor procedures with adverse effects below the above threshold, if they are part of a series or combination whose cumulative adverse effects are above the threshold for regulation;
- procedures performed wholly under general anaesthesia;
- procedures for generation and breeding of animals likely to suffer adverse effects, i.e.:
  - breeding animals with harmful genetic defects;
  - manipulation of germ cells or embryos to alter the genetic constitution of the resulting animal; and
  - subsequent breeding of such genetically modified animals.

6. Any expected adverse phenotypic expression in harmful mutant or genetically modified animals is included.
7. Costs arising from both acts of commission, e.g. dosing or sampling, and omission, e.g. withholding food or water, are considered.
8. Costs are assessed with reference to the biology, behaviour and life-style of the species concerned: for example, although partial facial weakness may be a relatively minor adverse effect in humans, it has serious consequences for cud-chewing animals.

Box 5: Factors described by the Home Office in the assessment of costs

- **Species and stage of development of the animals involved**
- **Nature and extent of all the likely adverse effects**[1] **on the animals,** due to all interventions from the time that the animals are issued from stock, until they are discharged from the control of the Act
- **Measures proposed to prevent or minimise the extent, duration and incidence of adverse effects,** including anaesthesia, analgesia, specific husbandry practices[2], observation schedules to facilitate early detection of problems, treatment of any animal suffering adverse effects, and any other appropriate measure
- **Humane end-points to be applied,** and the relevant clinical signs that will trigger implementation of these end-points[3]
- **Estimated number of animals to be used**
- **Fate of the animals at the end of the protocols:** method of killing; or continued use or re-use, release into the wild, or re-homing[4]
- **Source of animals:** (a) when non-human primates are acquired and used from non-designated sources, conditions at the holding centre in the country of origin are considered; (b) adverse effects due to capture and confinement of wild-caught animals are included; and (presumably) (c) for certain species, any adverse effects caused by use of sources other than those designated under the Act are considered
- **Transport arrangements for primates obtained from non-designated sources**
- **For some 'field studies', the incidental effects on the local ecology**
- **Whether there is any further scope for application of the Three Rs:**

– has adequate, active consideration been given to using non-sentient alternatives and identifying the optimum reduction and refinement strategies?
– is there justification for use of the particular species? If it is proposed to use non-human primates, dogs, cats, equidae, endangered species or animals taken from the wild is any alternative possible?
– is the use of Old World, rather than New World primates specifically justified?
– are the various methods integrated into a coherent programme of work, with, 'staging' where appropriate, so that *in vitro* precedes *in vivo* work for example?
– have the protocols been fully refined and all appropriate measures taken to mitigate adverse effects?
– will the most appropriate and humane end-points be applied?
– has suitable provision been made for ending suffering as soon as the welfare end-point is reached?
– if substantial severity protocols are involved, has the lack of milder alternative methods been specifically demonstrated?
– is any departure from Home Office guidance on minimum severity protocols justified?
– if post-operative analgesia is not given, is this justified?
– have the Named persons been consulted during the drafting of the application?
– will the minimum number of animals be used, consistent with the objectives of the work[5]?

1 See 4.3 below.
2 See Box 4 for definitions.
3 It is noted that these should be described in terms meaningful to those who will be responsible for monitoring the welfare of the animals.
4 Particular conditions apply in all these cases.
5 Minimising suffering takes precedence over minimising numbers, in that use of more animals in a milder severity protocol would be better than using fewer animals in a more aggressive protocol.

4.3.1 Clarifying the definition of cost

The Home Office defines costs as the adverse effects experienced by the animals used during the course of a study. It is important to recognise that a description of the costs of a study should not be simply a description of what will happen to the animals, but of what this will actually mean for the animals in practice. For example, in a study in which rats are singly housed, the cost to the animals is not 'single housing' – that is merely a description of what will happen to the animals. Rather, the costs are the effects that this isolation might have on the well-being of the animals – effects such as lack of the comfort and stimulation that comes from social contact with other animals, boredom and perhaps frustration, and in some cases maybe even physical effects of self-harm.

Enumerating the full range of potential costs of a study in this way not only enables a comprehensive cost-benefit assessment to be carried out, but, even more importantly, helps to ensure that all possible steps can be taken to minimise each and every cost. For instance, in the above example, providing the animals with environmental enrichments that can keep them occupied and help to compensate for the lack of social contact might reduce or alleviate the costs of boredom and frustration, and avoid the costs of self-harm. For further discussion, see Chapter 5: 5.4.3.

It is important to remember that costs encompass social and psychological costs, such as fear, anxiety, loss of memory, confusion, and boredom, as well as more overt physical harms (Box 4, para. 2). Depending on the circumstances, these effects can mean as much, or even more, to the animals than physical suffering. As Universities Federation for Animal Welfare (UFAW) suggests, "it is likely that too little weight is given at present to some forms of mental suffering, for example, mental states such as boredom and other suffering resulting from solitary confinement or changes in the social housing of animals", and everyone involved needs to be alert to the full range of potential adverse effects.

Costs can arise not only from acts or omissions that cause harms to the animals, but also from pleasures denied - that is, from withholding something that might have a beneficial effect on the animals. For example, "the absence of something the animal would desire - such as freedom or the ability to indulge in natural behaviour - can constitute an adverse effect" (BUAV).

Although in assessing costs the focus is usually on adverse effects that the animals experience, in that they are aware of them, there may be harms that the animal is not aware of, that should also be factored in to the cost-benefit assessment. For example, although an animal may not be aware of a small tumour growing inside it, it can be argued that a harm has nevertheless been done to that animal, if the tumour has been induced. Similarly, if an animal is injured, or is subjected to surgery other than for its own interest, it is harmed, whether or not suffering is involved. Anaesthetic removes the suffering, but it does not remove the harm.

We take the view that, roughly speaking, an animal is harmed if it is made worse off. Suffering and harm can be distinguished: an animal can suffer without being harmed – for example, when undergoing painful treatment for an injury. But an animal can also be harmed without suffering. Any pathological condition or injury inflicted on an animal (other than for its own good) would seem to constitute a harm whether or not any suffering is involved.

4.3.2 Additional costs

Some costs are not included in the Home Office criteria and are not required to be included in project licence applications. The most important of these additional costs are those caused by transport of animals. Currently, only the adverse effects of transport of non-human primates are considered - yet "prolonged transport is also a problem for animals such as genetically modified mice which

have often been developed in and therefore must be transported from mainland Europe or the United States" (LASA), or even further afield. **Costs due to transport of *all* species should be included in cost-benefit assessments carried out under the Act. This is particularly important in light of comments in 4.3.1 above - since, in order for such costs to be minimised, they must first be recognised.**

Other additional costs mentioned in responses are those caused to animals not directly involved in licensed studies. These include costs incurred during the lifetime of breeding animals which produce the animals used in research and testing (for example the lifetime confinement of breeding bitches), and the deaths of unused stock animals (RSPCA). It is difficult to see how the latter costs could be evaluated prospectively (only retrospectively). Nevertheless, **contingent harms such as those caused in animal breeding are clearly a part of the overall costs to animals of any given project, and should be identified as part of the cost-benefit assessment, especially in order that they can be minimised[1].**

4.3.3 Weight given to factors other than those associated with the actual scientific procedures

Many commentators, from a range of perspectives, suggest that more consideration should be given to costs due to capture, confinement, transport, husbandry systems and general handling.

For example, husbandry and care factors can often influence the overall harms to animals as much as the procedures themselves. Most of the time, animals are simply 'maintained' in the animal facility, so any husbandry costs can be a significant factor in the overall costs of a project. This is the case, too, for animals that are not used in licensed work, but are maintained in the animal facility until they are killed and used as sources of tissues and organs for *in vitro* work. Considerable suffering can be caused to animals by "environmental costs" such as "inability to express normal behaviour, lack of environmental enrichment, removal from the natural environment and transportation" (Animal Health Trust - criteria used by their ERP). Similarly, wider factors to do with the quality of facilities and the training and competence of those carrying out the procedures can sometimes determine the severity of the impact on the animals as much as the nature of the procedure itself.

Training and competence is specifically addressed as part of project and personal licensing, but the other factors are not mentioned explicitly in licences. Project licence applications cover animals from the time they are issued from stock – except where primates are concerned, when source and transport arrangements are specifically included. General standards of husbandry and care and quality of facilities are addressed as part of Certificate of Designation licensing of establishments, but are not specifically addressed in the context of particular project licence applications.

Wider factors such as capture, confinement, transport, husbandry systems and general handling of animals are clearly relevant considerations in the assessment of costs and should be taken into account in the cost-benefit assessment.

More explicit recognition of such wider aspects of cost should help to ensure that strategies are put in place to minimise their adverse effects on animals. In this context, some practical responses to the wider factors related to costs associated with animal use would include, as a matter of course:

[1] One respondent raises what they consider to be an anomaly in the assessment of costs to animals. Capture of wild animals during, or for use, in research does not require authority under the Act, except where anaesthesia is used. This situation is criticised on grounds that it does not reflect the degree of suffering likely to be experienced, since "the decision to use anaesthesia depends on the size of the animal and the likelihood that it may harm the experimenter, rather than on any intrinsic differences in costs to the animal concerned" (University of Sussex). Currently licences to trap birds are issued by the British Trust for Ornithology and those to trap mammals by English Nature, and are subject to different considerations when compared with the Act.

- thoughtful acclimatisation of animals, including familiarisation of animals to noises and routines within the animal unit or the specific area of use;
- socialisation programmes for primates, dogs etc;
- housing and care systems designed to make appropriate provision for the physical and psychological well-being of specific species (and strains) of animals.

Further measures might include screening animal room equipment (electronic instruments and caging) to minimise generation of potentially stressful ultrasound.

4.4 Factors in the assessment of benefits

Box 6 below collates the factors that the Home Office takes into account in assessing the importance of the objectives of scientific work involving animals - that is, in assessing its potential benefits. This list has been compiled from the three Home Office guidance documents noted in 4.2.1 above. Note that the Act limits the purposes for which animals can be used under its terms (see para. 1.1 in Box 7).

Box 6: Factors considered by the Home Office in assessing potential benefits

- Is the work original - does it offer a new approach or fresh insight in relation to existing knowledge? If the work, in whole or in part, is seeking to reproduce or repeat earlier work, has sustainable justification been made?
- Are the objectives:
  - Realistic - not over ambitious, specific, measurable, achievable, focused, likely to be funded?
  - Relevant - having links with and implications for other research?
  - Timely - relating to issues of current or developing interest or concern?
  - Able to be reviewed and evaluated?
- What is the significance of the project's potential benefits - in terms of:
  - *human, animal or ecological benefits*: improved health or welfare[1], plant production, food hygiene, safeguarding the environment; and/or
  - *scientific benefits:* resolution of controversies, increasing scientific knowledge; and/or
  - *educational benefits:* meeting educational objectives that cannot be satisfied by using non-animal methods; and/or
  - *economic benefits:* conservation of natural resources, cheaper healthcare for all (but not the profitability of the company carrying out the work, nor researchers' career prospects)[2]; and/or
  - other: e.g. forensic benefits.
- Is every effort made to maximise the expected benefits? (No useful data should be ignored or discarded).
- Is the project relevant to progress in the field of research in general?
- Will resources and findings be shared with others?
- How will the data or other material produced be used?
- Are there any potential disbenefits that should be considered[3]?

Notes:

1 See also more detailed criteria suggested in responses, listed in 4.4.

2 Whether such economic benefits are admissible is controversial - see 5.10 for discussion.

3 Home Office guidance asserts that potential 'disbenefits' (that is, "the potential for misuse of the resulting information or technologies") do not form part of the cost-benefit assessment *per se*, but also says that disbenefits are, nevertheless, considered as part of the review of new project licence applications. "When foreseen, they must be clearly signalled in the advice offered to the Secretary of State to facilitate the necessary wider consultation and consideration" (Home Office 1998a).

The criteria listed in Box 6 should not, indeed most cannot, be applied in a quantitative manner. They are intended as a guide to thinking, which can assist in arriving at informed judgements (see also Ch. 5).

The questions about scientific validity listed in Boxes 2 and 3 in Chapter 3 are also important factors in the context of assessment of benefit. Examination of these criteria can help in evaluating the likelihood that the potential benefits will actually be realised in practice, and whether and how far the particular uses of animals can be considered necessary to achieve the objectives. The Home Office clearly considers that scientific validity and benefit assessments overlap in this way, since "the essential determinants of 'benefit' remain the likelihood of success, and how the data (or other product) generated by the programme of work will be used" (Home Office 1998a and 2001). Examination of the other published schemes and respondents' comments suggests that the Home Office criteria are largely comprehensive and sufficient at present. However, a few responses suggest additional or expanded factors:

(i) Several organisations which use animals for applied animal research directed at human or animal disease suggest more detailed criteria for assessing the benefits of this kind of work (e.g. Animal Health Trust, and Royal College of Physicians of Edinburgh). The factors include:

- the nature and severity of the condition to be treated, e.g. the frequency and level of suffering associated with the disease;
- the clinical benefits of a successful treatment being developed from the work, e.g. reduction of pain or disability, increased quality of life, reduced loss of time from work, reduced side effects, more convenient treatment, cf. clinical values of current therapies;
- costs to humans of the disease in various terms, e.g. effects on longevity and quality of life, financial costs to health care providers (NHS, carers etc); economic costs of current treatments;
- the probability that the results will be able to be applied to the condition;
- benefits in terms of protecting the safety of patients and healthy volunteers;
- avoidance of animal use or reduction of animal use in future stages of the research and development process, e.g. small-scale exploratory work to select the best species or doses for later larger-scale work; early in vivo screening to rule out compounds with unfavourable distribution, metabolism and pharmacokinetic characteristics and so avoid unnecessary animal work;
- new and/or better understanding of the disease process itself;
- the possibility that the data generated will contribute to the development of better models (including in vitro or computer models) and research tools.

(ii) A more radical suggestion is that retrospective citation analysis be used as part of the assessment of future proposals - a low citation rate for previous work would imply less/no chance of future work being licensed (People for the Ethical Treatment of Animals). In fact it can be argued that a variation on this idea is included as part of the assessment of validity / likelihood that benefits will result, since the 'track record' of the researchers is taken into account (see Box 3, Chapter 3).

4.5 Particular issues in the assessment of costs and benefits

Although most commentators feel that, with some provisos noted above, the *factors* for assessment of costs and benefits set out by the Home Office are satisfactory, a number of issues relating to the *application* of the criteria are commonly raised. This is not surprising, since it is inevitable that this kind of methodology, which relies on judgements, will throw up problem areas. We have explored some of these more difficult cases as part of our goal of gaining a better understanding of how cost-benefit

assessment should be approached. In highlighting such areas, we do not imply that the whole process of cost-benefit assessment is problematic. Rather, we use the difficulties to illustrate the depth and comprehensiveness of the analyses required in cost-benefit assessment. Many of these areas could be subjects of whole chapters, or even separate theses. Here we simply offer brief descriptions of the issues as we see them, and, where relevant, suggest further questions that should be asked as part of the cost-benefit assessment - but we do not necessarily attempt to prescribe solutions.

4.5.1 Attitudes to different species of animal

Under the Act, special justification is required for the use of cats, dogs, equidae (horses, donkeys etc.) and non-human primates. Further than this, since 1996, the Home Office requires special justification for the use of Old World, as opposed to New World monkeys (e.g. special justification is required for the use of macaques rather than marmosets). Distinctions between species are also drawn by use of the terms "lower" and "higher" species (of mammal) in some of the official guidance on cost-benefit assessment. Several respondents suggest that such distinctions are arbitrary and even, what they term, "speciesist" (Association of Veterinary Teachers and Research Workers).

Evaluating the moral status of different species in this way is clearly difficult and highly contentious; and, moreover, is likely to be influenced by the context in which the animals are encountered and/or used. However, **it is clear that the Act's requirement for special justification for use of certain species should not be taken to imply that the costs of using other species, such as mice, ferrets or pigs for example, are *necessarily* less, all other things being equal. It is important to consider the particular needs of the particular animals involved, and to be sensitive to the likely effects of experiments on the individuals used.**

4.5.2 Assigning severity limits and bands

Home Office *Guidance* on the operation of the Act requires that assessments of likely costs to animals are classified into different levels of severity: mild, moderate, substantial or unclassified. There are two distinct applications of this classification, to:

> each **project**, which is assigned an overall *severity band*; and
> every **protocol**[2] within the project, which is given a *severity limit*.

The Chief Home Office Inspector's notes and the *Guidance* on the Act make it clear that it is the overall severity band which is weighed against the likely benefits of a project in applying the cost-benefit assessment (Home Office 1998a and 2000c, para. 5.47).

The severity limit

The severity limit of each protocol (e.g. oral gavage; induction of Parkinsonism) reflects the maximum level of anticipated adverse effects that an individual animal *may* experience as a result of the protocol, i.e. it reflects the *upper limit* of suffering for any animal undergoing that procedure. Examples provided by the Home Office (2000c) to illustrate how the severity limits are categorised include:

- *Mild* – for protocols that, at worst, give rise to slight or transitory minor adverse effects, e.g. small infrequent blood samples, minor surgical procedures under anaesthesia such as small superficial tissue biopsies;
- *Moderate* – e.g. toxicity tests that do not involve lethal end-points, many surgical procedures, provided that suffering is controlled and minimised by effective analgesia and post-operative care;
- *Substantial* – for protocols that result in a major departure from the animal's usual state of health and well-being, where one or more animals will be

[2] A procedure or series of procedures carried out on an individual animal or group of animals for a single specific purpose within the context of the project.

so affected - e.g. major surgery, some disease states where welfare is seriously compromised, acute toxicity tests and some efficacy tests of anti-microbials and vaccines that may involve significant morbidity or even death as an end-point;

- *Unclassified* – for protocols performed entirely under general anaesthesia, from which the animal does not recover consciousness.

The severity band

The overall severity band for the project as a whole is intended to reflect the degree of suffering likely to be experienced by the *average* animal used in the project (Home Office 1998a), and again is categorised as mild, moderate, substantial or unclassified. The *Guidance* on the Act (Home Office 2000c) notes that the severity band reflects the number of animals used in each protocol and the actual suffering likely to be caused as result, taking into account the proportion of animals expected to reach the severity limit of the protocol, the duration of exposure to that severity limit, the nature and intensity of the adverse effects and the actions taken to relieve suffering. On this basis, a project containing ten mild protocols, each involving 10, 000 animals, and one protocol with a substantial severity limit involving fifty animals, could well be classified as mild.

A number of difficulties are inherent in this classification of severity. Some of these arise because different people have different views on, and perceptions and interpretations of, the terms 'adverse effects', 'suffering', 'severity', 'mild', 'moderate', and 'substantial'. Others are a consequence of the different ways in which severity limits and bands are used in practice.

Interpreting the categories of severity

There is particular concern about the distinction between substantial and moderate severity. Substantial severity covers only the most harmful of all licensed work, in which significant long-term morbidity, or mortality could well occur, though not necessarily intentionally. The moderate category, by contrast, appears to be something of a catchall, covering a wide range of the more invasive procedures. A variety of procedures that, to many commentators, seem to have the potential to cause substantial suffering are classified as moderate.

In order to distinguish more clearly the wide range of levels of severity that is encompassed by the term 'moderate', we recommend that this category of severity be sub-divided.

An additional restriction on severity arises from the requirements of Section 10(2A) of the Act, in that "the Secretary of State will not license any procedure likely to cause severe pain or distress that cannot be alleviated" (Home Office 2000c). This gives rise to another difficult distinction, since it is unclear where the boundary between "severe pain or distress that cannot be alleviated" and "substantial severity" lies. Substantial protocols must include definition of the intended end-point, that is the upper level of suffering and the length of time that this is allowed to occur before it is alleviated, either by appropriate treatment or by killing the animal. The additional restriction thus means that a procedure which sets out to cause severe suffering that cannot be alleviated (i.e. a procedure without a defined end-point agreed by the Home Office) will not be licensed. Nevertheless, there are likely to be differences of opinion on what is to count as severe suffering that cannot be alleviated. For example, some people would consider that a procedure that causes substantial suffering leading to morbidity over a three day period before an animal is killed (and thus the suffering alleviated) would come into the category of severe suffering that cannot be alleviated and so should not be licensed. However, in practice, such a procedure might be granted a licence because the intention is to kill the animal before morbidity becomes death.

It would be very helpful if there was more material to illustrate how the severity classification system

operates in practice, and so enhance transparency. **In particular, we recommend publication of:**

- **more examples to illustrate what counts as mild, moderate and substantial severity than currently appears in the Home Office Guidance on the Act, so as to enable wider understanding of what each category actually means for the animals that experience it; and**
- **information about how the limits and bands are interpreted, assessed and used by people working under the Act and by the Home Office.**

The criteria used to define the levels of severity should be regularly reviewed in the light of increasing understanding of the nature of animal suffering, and such publications updated accordingly.

Purposes of severity limits and bands

The severity limits and bands seem to be used in three main ways:

(i) *Managing projects:* The severity limits of protocols are used as part of strategies for management and minimisation of adverse effects on animals. Placing a protocol in the moderate rather than the substantial category requires licensees to intervene earlier to alleviate the adverse effects in animals and/or to establish less harmful end-points at which the animals must be killed;

(ii) *Encouraging deeper thought:* The words mild, moderate and substantial are quite 'pointed' and assigning projects and protocols to the different levels of severity can encourage licensees and others involved to think more deeply about the effect their experiments will have on the animals. In particular, most people would not set out to cause substantial suffering to animals without deep thought, and will make strenuous efforts to avoid protocols that are classified as substantial. Preparing a protocol for a moderate limit rather than a substantial one will require setting a lower limit of permissible suffering, and this should encourage a move to refined protocols, which require earlier intervention to alleviate suffering. For example, an acute toxicity test could be ended with minimal clinical signs after say four days, instead of allowing the toxic effects to develop to a stage at which the animal becomes moribund. However, the potential downside of this argument is that protocols labelled moderate (or mild) could engender less concern and therefore less motivation to refine them; moreover, as noted in *'Interpreting the categories of severity'* above, a moderate severity limit may not adequately reveal the actual level of suffering involved.

Both of the purposes (i) and (ii) are advantageous because they should make people think more about what they do and should motivate them to set lower limits. In this context, we have already recommended that the moderate category of severity should be subdivided to enable more accurate reflection of the degree of suffering likely to be experienced by the animals.

(iii) *A public information tool:* The number of projects falling into each overall severity band is published in the annual Home Office statistics of animal use. Currently, this is the only source of public information about the likely severity of adverse effects caused to animals in scientific projects. However, these overall bands can be misleading because they are assessments of the likely experience of the average animal, and therefore do not provide information about the maximum harm that individual animals within the project are permitted to suffer, or the proportion likely to experience such adverse effects. Moreover, because they represent prospective judgements the severity bands do not necessarily reflect the actual adverse effects caused to the animals in practice. Thus, for example, the number of

substantial band projects can give no indication of the numbers of animals that suffer substantially. Publishing such data is not, therefore, of much use in terms of providing public information about severity.

We believe that a new or revised system is required for recording the severity of adverse effects on animals for public information purposes (see Ch. 5: 5.5.2 for further discussion).

Severity bands and cost-benefit assessment per se
As noted, Home Office guidance suggests that it is the overall severity band of a project which is used for purposes of cost-benefit assessment. We believe that it is inappropriate to base cost-benefit assessments on what the 'average' animal will experience in a given project, because this assumes that mild costs to one set of animals (in a given protocol) can somehow mitigate more substantial effects in a different group of animals (a different protocol). As BUAV suggests, "this approach is liable to distort the cost-benefit assessment", particularly in wide-ranging project licences covering many different procedures and involving the use of large numbers of animals (see also Ch. 5: 5.4.4). In our view, the published descriptions of how the overall severity banding is arrived at and used in cost-benefit assessment belie the complexity of the judgements that are actually made. In practice, a series of more sensitive judgements has to be made, on a protocol-by-protocol, as well as a whole project basis. If the severity of any of the protocols, in light of its benefits, gives cause for concern, then that protocol will have to be amended or removed altogether, in order for a licence to be granted. Given that this is the case, we believe that the assigning of an overall severity band is both superfluous and misleading.

We conclude that overall severity bands are inadequate both for purposes of cost-benefit assessment and providing public information about severity. On these grounds, we doubt the value of assigning overall severity bands for projects, and invite the Home Office to consider reviewing the utility and effectiveness of severity banding for assessing, monitoring and managing projects. Furthermore, we believe a new or revised system should be put in place for public information purposes. See '*Purposes of severity limits and bands*' (iii), above, and Ch. 5: 5.5.2, for further discussion.

4.5.3 The weight assigned to 'death of an animal' in itself (i.e. in absence of suffering)

As might be expected, views on whether and how far the costs of humane killing of animals should be included in cost-benefit assessment tend to polarise. Many respondents feel that, although "animal life should not be taken wantonly, a humane death cannot be given the same weight as other factors in the cost-benefit assessment" (MRC). This view is taken for a variety of reasons:

- "the cost-benefit assessment has to reflect the value that society as a whole places on animal life and suffering - society accepts the taking of animal life more freely than it accepts suffering" (MRC);
- similarly, the focus of cost-benefit assessment should be on suffering. "Death by a humane method does not cause suffering and therefore should not be included in the cost-benefit analysis" (Anon.);
- the majority of laboratory animals would not have a life in the first place if they were not specially bred for research (Royal College of Physicians and Surgeons of Glasgow) (see also Ch. 2: 2.2).

In contrast, other respondents believe that animal life has intrinsic value and so even a painless death can constitute a cost. Some take this as self-evident. Others offer reasons. For example, Uncaged Campaigns argues that "death is the ultimate, irrevocable harm", because the lives of

sentient animals are valuable, both in themselves, in that "all animals strive to sustain and protect their own lives", and to others, including the humans who care for and value them. The RSPCA makes a similar point: "death should be considered a harm and should be given serious weighting since presumably an individual animal that is not suffering substantially would not actually choose to give up his or her own life".

The "Reduction" strategy demanded as part of the Three Rs also seems to assume that the death of an animal is a cost in itself. Reduction of animal use appears to be required, not simply in order to reduce the amount of animal suffering in procedures, but also to reduce the number of animal lives that are taken.

Respondents who hold both of the general views described above point to a variety of indirect harms that can be caused by death of an animal and that might be factored in to the cost-benefit assessment. These include:

- the psychological effects on humans of killing animals, particularly large numbers of unused animals;
- the effects on mother animals of removal of their offspring;
- the effects on social groups of animals when one or more members are removed and killed;
- adverse effects caused when the killing is not carried out competently.

However, whilst these potential harms are important and should be considered within the cost-benefit assessment, they are not relevant to the question of whether death in *itself* is a harm.

4.5.4 Costs related to genetic modification of animals

Although many commentators argue that the genetic modification of animals raises no new categories of cost, a number (from a range of perspectives) suggest that this technology raises concerns about the severity of costs and the difficulties encountered in assessing them both prospectively and comprehensively.
Cost-benefit assessment needs to be sensitive to such concerns, which include the following:

- the numbers of animals that have to be used and bred to generate relatively few genetically modified animals that are of scientific value or interest. This is a concern in large-scale projects involving production of genetically modified animals and also the generation of random gene mutations in mice in an effort to develop new models of human disease (see 4.5.5 below for further discussion);
- difficulties in assessing costs prospectively, because of the often unpredictable and unanticipated phenotypic effects of genetic modifications (the same difficulty therefore applies in the assessment of benefit, see below);
- the level of commitment that is given to assessing fully the effects of genetic modifications on animal welfare, because attention is often focused only on that part of the animal that is of scientific interest - this means that the cost-benefit assessment cannot be fully informed, even retrospectively;
- a need to enhance implementation of the Three Rs in the techniques used to generate genetically modified animals and to reduce 'wastage'.

For further discussion of these and other aspects, see the report of a recent BVA:AWF/FRAME/RSPCA/UFAW joint working group on refinement (Robinson *et al*. 2003, in press).

On a more positive note, it is also suggested that in certain circumstances the use of transgenic as opposed to conventional animals could, in the future, help to reduce the use of animals in some areas. For example "humanisation" of rodents by insertion of genes for human drug receptors could reduce the need to use non-rodent (second) species

in some toxicity tests of pharmaceuticals (Anon.). However, it is uncertain how far this is likely, because it can also be pointed out that, since the rest of the animal is unaffected by the genetic modification, the need to examine the wider systemic effects of pharmaceuticals, which at present involves the use of second species, will remain. See discussion in Boyd Group (2002a).

4.5.5 Difficulties in predicting the benefits of genetic modification (including mutagenesis) intended to produce new animal models

The APC's biotechnology report (Home Office 2001b) acknowledges that there can be difficulties in predicting and assessing the validity of animal models for human disease, especially because the models usually only provide analogues of the diseases, many of which do not occur naturally in non-humans.

Attempts to produce new animal models, whether by selective breeding or genetic modification can have unexpected and unintended consequences. Genetic modifications, in particular, can be difficult to control precisely, and "their unpredictable effects make it difficult to carry out a precise cost-benefit assessment" (University of Sheffield). "The effects of transgenesis or of the cross-breeding of different transgenic lines may be unpredictable, and in the event the resulting phenotype can be unrelated to the scientific justification for producing the animal in the first place" (RSPCA).

On the other hand, we also note that "transgenesis permits more precise animal models to be developed and may improve scientific insight, while often reducing the severity or procedures used in existing animal models" (Anon.). Indeed, several respondents give specific examples of clinical and other benefits that have resulted from the use of genetically modified animal models – see Annex E. Large-scale projects involving the generation of random gene mutations in male mice by treating them with a chemical known as ENU (N-ethyl-N-nitrosourea), in an effort to develop new gene-based mouse models of human illnesses, pose even greater difficulties for predicting benefits. For each useful model that results, large numbers of mutant animals that do not have 'desirable' mutations are likely to have been produced. Some of these animals will bear mutations that cause relatively trivial effects (such as an unusual coat colour, or size larger than average), but others suffer more serious conditions. The difficulties in predicting outcomes in such cases make prospective cost-benefit assessment, as required under the Act, very difficult.

The RSPCA comments that "it is unacceptable to create GM animals simply because the technology is there", arguing that there needs to be more critical review of scientific and clinical necessity to produce such animals, and critical on-going and retrospective review of the outcomes of the work. However, it is difficult to see how this can be achieved when some licences for production of GM animals allow such a broad range of potential applications. As already noted, the question of what constitutes an appropriate scope for a project licence, to enable proper application of the cost-benefit assessment, is taken up in Chapter 5.

4.5.6 On assessing the benefits of 'fundamental' research

Inevitably, there are uncertainties in predicting how valid and useful the results of experiments will turn out to be - no matter how good the experimental design. "Clearly if the outcome could be known with certainty, the experiments would be irrelevant" (Anon.).

Many respondents say that the "benefits of fortuitous discovery" noted in paragraph 8 of the consultation document are not valid reasons for using animals: "Creating an opportunity to make fortuitous discoveries is not a valid reason for carrying out an [animal] experiment" (Physiological Society). However, there seems to be a (subliminal,

and not very clear) distinction being drawn between this and "curiosity driven research", that "may produce extremely important information that can have enormous impact many years down the line" (Anon.).

The "advancement of knowledge in biological or behavioural sciences" is a permissible purpose under Section 5(3) of the Act. Moreover, under the Act, such gains in knowledge are considered to be intrinsically valuable, and do not have to be instrumentally beneficial in order to provide an acceptable reason for using animals. In other words, they are considered to be actual benefits; they are not being judged simply on the basis of the potential or possible benefits to which they might lead.

However, assessing the value of actual gains in knowledge, in the absence of any envisaged practical application of the results, in such a way that this value can be weighed against the harms to animals, can be troublesome – at least for some people. This is particularly so where costs to animals are perceived to be high (for example, where use of non-human primates is concerned), and where further practical benefits are judged possible rather than probable.

In practice, "the full [instrumental] benefits of basic research can only be assessed over long periods of time" (MRC). However, it is often forgotten that this is also frequently the case in research that is said to be applied - that is, directed towards the solution of a particular problem, or with a particular practical application in mind. In many applied areas of animal use, each licensed research project is likely to generate a small part of the knowledge needed to solve the problem in view. By the same token, although particular practical applications are not envisaged in research classified as fundamental, such research is usually carried out in areas identified as being of strategic importance, in which better knowledge can influence work more obviously directed at a practical application. For example, work to understand central nervous system receptor sites for chemicals produced in the brain could be classified as fundamental research, because the work is not directed towards any clearly identified practical application. But it is nevertheless apparent that the knowledge generated by such work could be used in research that is directed towards particular health care benefits in the future. As Home Office guidance also points out, viewed this way, the gap between fundamental and applied research is much narrower than might commonly be imagined.

Fundamental and applied research, therefore, are intimately related and, in practice, interact and intermingle. If the antecedents of any particular instrumental benefit are traced, there will almost always be fundamental as well as applied research findings involved. Gains in knowledge can be particularly valuable because they add to the information that is available to be used and built upon in pursuit of particular applications. The benefits of such fundamental knowledge therefore depend on its strategic value - its links to and implications for other areas of research (fundamental or applied) - and, in particular, on whether it is communicated, disseminated and used in practice.

4.5.7 Taking into account the likely benefits of substances subject to regulatory tests involving animals

Regarding Home Office assessment of the benefits of using animals to develop and test new materials and products, "a clear distinction is made between the research and development of new materials and products, and regulatory toxicology and safety testing". When new products are being developed, "the utility of the new material is one of the main determinants of benefit". Whereas in toxicity and safety testing, the benefits are viewed in terms of "the need to facilitate sound regulatory decisions for the protection of man and the environment,

rather than on the utility or benefit of the end-product" (Home Office 1998a and 2000). (Note that the benefits of legally required efficacy testing are regarded in the same way as regulatory toxicity testing.)

We support the RSPCA's conclusion that this distinction:

"is a convenient way of avoiding conflict between different legislative requirements. However, it prevents consideration of the true balance of costs and benefits in the testing of particular types of product. If the utility of the new material is a determinant of the cost-benefit analysis for development tests, it should also be a determinant in the analysis for safety testing. A ban on the animal testing of household products has been suggested a number of times because the benefits of more of these products are not seen to outweigh the costs to animals of testing them. This has understandably foundered on the definition of household products. This problem might be solved if a cost/benefit analysis of testing requirements was carried out on all substances on a case-by-case basis. Questions could then be asked about the benefit/value, for example, of an improved colour or perfume for use in cleaners or deodorisers. No doubt this would evoke criticism from industry, regulators (and even some consumers) with respect to stifling innovation, restricting freedom of choice, and so on. There is also the practical question of which Government department would be responsible for such a decision – those who regulate animal experiments or those who create the demand for the tests? Nevertheless, it would be useful to explore, and lay out clearly, what the implications of such an approach might be, and what the real obstacles are to performing a 'genuine' cost/benefit analysis for the testing of chemicals".

4.5.8 Duplication of animal experiments

As noted, 'originality' is a factor in the assessment of benefit, in that, to be judged acceptable under the terms of the Act, scientific research involving animals has to offer a new approach or fresh insight in relation to existing knowledge (see Box 6). Such insight can include better understanding of the reliability of knowledge derived from previous studies – and gaining this understanding might involve reproducing or repeating the earlier work in whole or in part. As Box 6 suggests, this kind of replication is a legitimate use of animals under the Act, provided that specific, sustainable, scientific justification is provided.

A number of responses to our consultation, however, argue that animal experiments are sometimes repeated without adequate, sustainable scientific justification and that this causes unnecessary and unjustified duplication of animal use. Examples include accidental duplication occurring through ignorance of others' work, and duplication for reasons of commercial confidentiality, or in similar studies run concurrently.

Accidental duplication of previous studies

Unjustified duplication of previous studies should be avoided through rigorous review of the existing scientific literature, prior to proposing 'new' studies. However, avoiding all such duplication can be difficult, since the results of many animal studies never make it into the pages of scientific journals – because, for example, they are 'negative' (e.g. they fail to prove a hypothesis), or lead to a 'blind alley' (such as occurs when a possible novel drug candidate is found unsuitable and discarded). Scientists should be able to obtain some information about such negative studies through more informal knowledge of their area of interest and communication with peers. But the information gained in this way may not be comprehensive, and more publication of negative results could also be of assistance.

Duplication and commercial confidentiality

Unnecessary duplication of safety and efficacy tests,

when adequate data already exist, is a particular concern in this context. Commercial competition can be a barrier to data sharing, and data are often classified as confidential within companies, so that tests may be duplicated because companies are unaware of and/or cannot gain access to data that other companies and the regulatory authorities hold. For example, "generic" pharmaceuticals, pesticides and other products are identical, or bioequivalent, to brand named counterparts, but are usually sold at substantial discounts. They can be manufactured and marketed when the patent protection afforded to the original branded products expires. Because the generic and brand name substances are identical, there should in theory be no need to repeat animal tests for any generic products. But this depends on the willingness of the originator to grant access to the relevant data - and access is not always forthcoming. Similar concern arises in the case of 'me-too' pharmaceuticals and other products, which are similar but not identical to the original brand names, and can therefore be manufactured and marketed whilst the original products are still under patent protection – but more usually are formulated when the original patents expire. However, in this case, the Chief Inspector comments that because the formulations are seldom if ever identical, data establishing equivalence, safety, efficacy and quality maybe required and the original datasets do not satisfy the relevant regulatory authorities.

As part of the argument that the duplication of tests is unnecessary, the benefits of developing generic and me-too substances are also questioned. These benefits are generally viewed in terms of providing choice and lower costs – which, in the case of pharmaceuticals would be lower health care costs – as well as economic benefits to the companies concerned. This raises the question of how far a largely economic benefit can be considered a legitimate part of the cost-benefit assessment (see 4.5.9 below). What might, at least, be said here is that the nature of the substances tested should be taken into account in the cost-benefit assessment, not just the benefits of the tests in terms of safety (see 4.5.7 above), and that every effort should be made to eliminate duplicate animal testing.

The UK Interdepartmental Concordat on Data Sharing[3] is intended to address the problem of duplicate testing across the board, but the scheme is voluntary and has only just been set up, and it is unclear how well the Concordat will work in practice. Under the EU Dangerous Substances Directive, companies contemplating testing a new chemical ingredient are required to contact their national Competent Authority (in the UK, the Health and Safety Executive (HSE), and Environment Agency acting jointly) to enable a search to be conducted of substances that have already been tested, with the intention of minimising animal testing by sharing existing data wherever possible. If data sharing is possible, the two companies are made aware of each other and also informed that the UK Competent Authority discourages repeat testing in such circumstances. However, where data sharing cannot be agreed, the UK regulations do not permit the sharing to be imposed. The HSE reports that over the past 8 years around 1 in 10 of the *circa* 100 searches carried out annually result in positive identification of opportunities for data sharing, a "significant number of which lead to data shares" (personal communication).
The comments of the Pesticides Safety Directorate (a regulatory authority) in response to our consultation show just how difficult it can be to avoid duplication in practice. PSD considers that the "generation of data packages for generic pesticides, i.e. the generation of a new package of animal studies when one exists but no access is granted by the holder" is an experimental purpose that is not justified. However, "unfortunately,

[3] See <www.homeoffice.gov.uk/animalsinsp/reference/data_concordat/index.htm#fnret1> for this document.

although our legislation does allow us some action in this area, the ultimate step of imposing a settlement would be extremely difficult and would require monetary compensation to be awarded. Unless and until other Government departments agree on how regulators can act as honest brokers, the best we can do is run a system that encourages and does not inadvertently prohibit data sharing". BUAV asserts that "commercial concerns are very unlikely to disclose information unless required to do so", and proposes that data sharing between companies, with compensation if necessary, should be compulsory rather than voluntary. This could be required by legislation or regulation at an EU level or nationally, but the mechanism for achieving this is not obvious.

Duplication in concurrent studies

Critics also assert that unnecessary duplication of animal experiments arises when similar experiments are run concurrently by different scientific teams. However, scientists respond that such studies are rarely, if ever, identical, and that, in any case, similar efforts by different scientific teams are part of the normal process of scientific discovery, which can be spurred along by competition to be first to reach the desired goal. Critics, on the other hand, rejoin that whilst this situation is perfectly acceptable in, say, the physical or chemical sciences, where work on insentient material is concerned, it is unacceptable in studies which involve taking animal life and/or causing animal suffering. There are clear differences of opinion about where the boundary between 'scientifically valid and justified replication' and 'unnecessary and unjustified duplication' of animal studies lies. The Chief Inspector comments that when the Inspectorate is aware that groups wish to develop common strategies for very similar objectives, efforts are made to encourage collaboration. One such example is given in the annual Home Office statistics for 1998 (Home Office 1999, p. 99, case 7). However, it is also observed that in such situations great care has to be taken to ensure that confidences are not breached, and the final decision on collaboration generally rests with the users.

Conclusion

Genuine duplication of animal studies, without strong and sustainable scientific justification, is unacceptable and should not take place. In the case of duplication as a result of commercial confidentiality, we welcome work on the new UK Interdepartmental Concordat, but it is too early to say how effective this will be in preventing unnecessary duplication of animal studies. The impact of the UK Inter-departmental Concordat on Data Sharing should be monitored carefully and reports placed in the public domain. If the Concordat does not prove to be effective, more binding measures, such as legislation, will be needed to achieve the Concordat's aims.

Avoiding unnecessary duplication in concurrent studies, or accidental duplication, depends in large measure on the diligence of researchers themselves – in particular, in seeking information from the results of previous studies and work in progress, and in critically evaluating the need for their experiments in light of that previous and on-going work. **In both industry and academia, researchers who propose and/or carry out animal work bear responsibility for avoiding unnecessary duplication of animal use, and need to employ considerable determination and imagination to ensure that animals are used *only* when sufficient useful and relevant data are unavailable.**

4.5.9 Is economic benefit a legitimate part of the cost-benefit assessment?

The Home Office comments that the profitability of a company plays no part in the assessment of benefit, but that the goal of cheaper healthcare for all is a legitimate reason for using animals, because of the effects on health, not on economics. No comment is made about whether or not economic benefits in terms of the employment provided by

companies and the wider social benefits that this brings should be included (this is a part of the 1993 note by the then Chief Inspector).
In our discussions we asked whether economic benefit can ever form a legitimate part of the cost-benefit assessment. The answer we believe, must be negative. It is true that human health and welfare figure in the list of permissible purposes for which animal experiments may be conducted. And it might be argued that economic benefits are not necessarily less valuable than other benefits in terms of human welfare. Furthermore, certain economic benefits, such as jobs and social prosperity, can be as important for health as more direct medical benefits. However, the Act does not countenance animal experiments just because they can produce permitted benefits. It is required to demonstrate that no reasonable alternatives are available.

4.5.10 Taking into account wider issues

Cost-benefit assessment *per se* does not address certain broader, more fundamental issues about where research priorities should lie, when that research involves the use of animals. For example, is it acceptable to use animals to develop pharmaceuticals that deal with diseases or conditions for which humans themselves could be said to be responsible –sometimes given the pejorative label "life-style" diseases?

Such diseases and conditions indeed pose challenges for cost-benefit assessment under the Act. Two considerations, in particular, are relevant. One stems from the requirement to show that there is no alternative to animal experiments if we are to find a means of alleviating or eradicating such diseases. For in the case of lifestyle diseases, it may be argued, there is a clear alternative – namely a change of lifestyle, or not adopting the lifestyle to begin with. The second consideration goes to the very heart of why society permits animal experiments in the first place. This is presumably because human health is judged to be of the highest priority, sufficient to justify animal suffering that would not otherwise be permitted. However, those who knowingly and voluntarily put their health at risk as a result of the way that they choose to live, demonstrate that they do not in fact concur with society's judgement in this respect. In their case, therefore, justification for such suffering might be claimed to be lacking. Clearly, there are wider, and difficult issues raised by these considerations that affect the provision of health care in general, and that therefore lie beyond the brief of this report. In any event, and for present purposes, we must presume that both considerations give way in face of the simple fact that most, if not all these diseases *can* occur independently of a person's lifestyle.

Some critics also assert that so-called 'disbenefits' (that is, the potential for research to have adverse as well as beneficial effects) is not taken into account in cost-benefit assessment. However, the Home Office says that it identifies such issues where possible and signals this to the Secretary of State who can initiate wider consultation. They should not be ignored, therefore.

4.6 Advance constraints on the scientific purpose and nature of animal use

4.6.1 The position under the Act

The Act defines and limits the scientific purposes for which animals might be used, but within these there are very few further *a priori* constraints on the scientific purposes and nature of animal use for which project licence applications can be made. Box 7 lists the constraints imposed within the terms of the Act, and in the qualified bans currently imposed via administrative controls introduced by the Secretary of State.

Other restrictions under the Act guide practice in the vast majority of cases, but also allow exceptions to be argued for. For example:

- the Act restricts the source and supply of animals that can be used in scientific procedures, in that,

under Section 10(3):

- dogs and cats have to be obtained from designated breeders;
- species listed under Schedule 2 of the Act (the commonly used species) have to be obtained from designating breeding or supplying establishments;
- no endangered vertebrates and no wild-caught animals can be used,
  unless, in any of these cases, the Secretary of State considers that an exception is justified[4]*;*
- under Section 10(2A) of the Act, all experiments must be carried out under general or local anaesthesia, *unless the Secretary of State judges that anaesthesia would be more traumatic to the animal than the experiment itself, or that anaesthesia is incompatible with the objectives of the experiment*[5].

In each case, decisions whether or not to grant exceptions will involve making judgements about the harms and benefits of deviating from the general, *prima facie*, conditions, whether alternatives are possible - and, therefore, whether any deviation can be justified.

In summary, little is absolutely ruled out under the Act. Rather, projects are judged case-by-case in terms of the balance of their likely benefits over their likely harms to animals, allowing flexibility in interpreting many of the general conditions set out in the Act.

Some respondents suggest that the principles underlying the various additional restrictions currently imposed by the Secretary of State are insufficiently clear, and that these are mere matters of opinion, that have not been properly argued for. The 1997 APC report also hints at this doubt (Home Office 1998a, para. 31, p. 48). Certainly, the detailed principles and arguments underlying the restrictions are not set out in any easily accessible official publication. However, the Chief Inspector gives three general reasons for the various constraints currently imposed by the Secretary of State:

- unjustifiable costs (use of Great Apes);
- alternative methods available (cosmetics testing, ascites production - and presumably manual skills training, except for practising microsurgeons);
- morally or ethically objectionable (tobacco, alcohol and offensive weapons testing and development) (Home Office 1998a, para. 3.5, p.52).

It is also suggested that the current restrictions have been set primarily for political reasons, and have had little impact on animals and their welfare. This is because they are perceived as trumpeting cessation of uses of animals which did not occur anyway (Great Apes), or which occurred infrequently and have in any case moved abroad in light of the ban (cosmetics testing). However, a more positive interpretation is that the restrictions formalised limits on animal use that already commanded widespread moral and practical consensus, and to which, it was widely agreed, there ought to be no return - at least in normal, as opposed to emergency, circumstances (see also 4.6.2 below).

The administrative restrictions are best viewed as the results of general, rule-of-thumb cost-benefit assessments. They are not written into the Act and, in theory at least, are open to challenge and change at any time. It is possible to submit a project licence

[4] Exceptions will only be granted when the Secretary of State is satisfied that no other animals are suitable and endangered species can only be used in research "aimed at the preservation of the species in question" or for "essential biomedical purposes where the species in question exceptionally proves to be the only one suitable for the purposes" (Section 10(3)).

[5] No experiment that causes serious injury or severe pain can be carried out without effective anaesthesia, and, if necessary, procedures without anaesthesia must use analgesics or other appropriate means to minimise the pain, distress or harm caused to the animals. This example is important, since the fact that flexibility is allowed here seems frequently to be misinterpreted by critics of the Act. Local or general anaesthesia must be provided for all surgical procedures, except for very minor procedures, where anaesthesia would be more traumatic to the animal than the procedure itself.

application in any of these areas for consideration by the Home Office Inspectorate, which will examine the case and decide whether or not to recommend to the Secretary of State that an exception be made.

4.6.2 Views on whether there should be further advance constraints under the Act

As noted, the Act allows the Secretary of State flexibility in deciding how the cost-benefit assessment will be implemented in practice and, with this, opens the way for the Secretary of State to impose any further general conditions / restrictions that he or she sees fit, taking into account the advice of the Home Office Inspectorate and of the APC when consulted.

Box 7: Current advance constraints on the scientific purpose and nature of animal use permitted under the Animals (Scientific Procedures) Act 1986

1 Advance constraints on the scientific purposes for which animals can be used:

1.1 *Constraints imposed by the Act itself:*

- animals can only be used for the permissible purposes listed in Section 5(3) of the Act, that is:
  (a) 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;
  (b) the assessment, detection, regulation or modification of physiological conditions in man, animals or plants;
  (c) the protection of the natural environment in the interests of the health or welfare of man and animals;
  (d) the advancement of knowledge in biological or behavioural sciences;
  (e) education or training otherwise than in primary or secondary schools;
  (f) forensic enquiries; and
  (g) the breeding of animals for experimental or other scientific use
- regulated scientific procedures on animals must not be performed as an exhibition to the general public or shown live on television for general reception (Section 16(1)).

1.2 *Restrictions currently imposed via administrative controls introduced by the Secretary of State:*

- at the Act's inception it was announced that project licences for training to develop or maintain manual skills will only be issued for training of practising surgeons in microvascular techniques, when no alternatives are available;
- in 1997 it was announced that licences will not be issued for:
  – testing finished cosmetics products and substances intended for use as cosmetics ingredients;
  – development or testing of alcohol or tobacco products (though the use of tobacco or alcohol as research tools can be considered and licensed in the context of investigating disease or novel treatments);
  – development or testing of offensive weapons (but licences can still be granted for developing and testing means of protecting people or treating the effects of weapons)[i].

2 Advance constraints on the nature of animal use:

2.1 *Limits imposed by the Act itself:*

- animals must not be subjected to severe pain, distress or suffering that cannot be alleviated (Section 10(2A))[ii];
- a neuromuscular blocking agent must not be used instead of an anaesthetic (Section 17 (b)).

2.2 *Restrictions currently imposed via administrative controls introduced by the Secretary of State:*

- in 1997 it was announced that licences will not be issued for the use of Great Apes (that is, chimpanzee, pygmy chimpanzee, gorilla and orang-utan)[iii].

i In 1999 the government announced that the LD50 test (OECD Guideline 401) will no longer be allowed in the UK, but the test can still be licensed on "exceptional scientific grounds" (though the insistence of a foreign regulatory authority does not constitute an exception to this rule).
ii 'Severe', however, is open to interpretation - see discussion in paragraphs 5.3 and 5.4.
iii In 1997, also, it was announced that use of the ascites method of monoclonal antibody production would only be permitted if, exceptionally, this proves to be the only possible method.

In evaluating the possibility that there should be further advance constraints on animal use under the Act, two points, in particular, have to be addressed:

(i) The strength of the case for any such restriction must be examined in detail. Arguments for and against must be comprehensively and critically assessed, with reference to:
   (a) the moral principles underlying a judgement that the particular use of animals is unacceptable under any normal circumstance; and
   (b) the likely consequences of the restriction - including consideration of the likely consequences for animal welfare, and what, if any, advances (in human or animal health and welfare and/or science) might be lost if the experiments were not done.

(ii) As part of the consideration of consequences, the possibility that any further unilateral ban on particular uses of animals in the UK will simply drive the work abroad must be taken into account. If work is taken abroad and scientific and/or animal welfare standards are possibly compromised, the net result could be an increase in costs to animals - possibly along with an increase in potential risks to humans and other animals if the results of the tests are scientifically invalid.

In relation to each of these two points, opinions are mixed on the desirability or otherwise of further absolute constraints on the use of animals under the Act.

For example, scientists and companies that use animals, as well as those funding such work, tend to take the view that flexibility is important and that the cost-benefit assessment should continue to be applied case-by-case with no further restriction. This is because it is asserted that:

(a) Where benefits are concerned, it is easy to reach false generalisations (Anon.). For example, although using animals to develop and test anti-obesity drugs for what could be termed lifestyle or cosmetic reasons might be considered unjustified, there are also recognised medical conditions that can be considered to warrant the use of pharmaceuticals, and the distinction between the two areas is not black and white (Anon.). Similarly, research into treatments for hair loss may have merit for cancer patients undergoing chemotherapy, even though treatments for hair loss are often considered vanity remedies (Association of Medical Research Charities).

(b) It is difficult to predict future needs (Anon.), so that, where costs to animals in particular are concerned, it is argued that it would be inappropriate to ban certain kinds of experiment, because there may later be a major, serious public health need to conduct research and the 'banned' category may be the only way of doing this.

In contrast, other individuals and organisations (mainly, but not exclusively from animal welfare and anti-vivisectionist perspectives) argue that the benefit of the doubts expressed in (a) should lie with the animals. If it is widely agreed that it is unacceptable to use animals in research carried out with the intention of addressing human problems that could be solved by a change of lifestyle, for example, then this use of animals should not be allowed, regardless of whether other benefits might result. Intention, it might be argued, is all important here. Paragraph (b) is probably something of a red herring, in that, under current arrangements, the Home Secretary could reverse or alter any of the administrative restrictions at any time, in order to respond to the kind of exceptional, emergency situation envisaged by those who wish no further advance constraints on animal use under the Act.

On the question of work simply being moved abroad following a ban in the UK, some commentators

argue that further advance restrictions under the Act could be both morally dishonest and inconsistent:

"The government is on thin 'moral ice' in deciding that some procedures or the use of certain species is 'morally objectionable' in principle... Indeed, the rest of the world could accuse the UK of applying a 'not in my backyard' principle, whilst accepting and exploiting the results of such work. They [the government] must accept that arbitrary bans of tests and species will simply mean that work is done elsewhere, possibly to lower welfare standards than are applied in the UK. If a vaccine against HIV is developed using Great Apes, will the government prohibit the use of the vaccine in the UK on moral grounds of the unacceptability of this research?" (Anon.).

Meanwhile, others assert that the possibility that animal work will be exported abroad should not prevent the UK from taking a unilateral moral stand. Indeed, several respondents go further, suggesting that researchers who carry out work abroad in order to "evade the strictures of UK legislation" should not be awarded licences under the Act.

4.6.3 Candidates for further administrative restrictions suggested by respondents

A number of individuals and organisations (mainly, but not exclusively, from animal welfare and anti-vivisectionist perspectives) suggest further uses of animals that they believe ought to be ruled out under the Act. The suggestions fall into three general categories:

1. *Animal procedures that some respondents consider unacceptable and unnecessary because they have been superseded by refined methods and/or do not conform with currently accepted best practice:*

Examples include retro-orbital bleeding, tube restraint of rodents and/or use of ether anaesthesia. For the same reason, the RSPCA also argues that husbandry and care that meets only minimum standards should be ruled out and that efforts should always be made to improve upon the minima. For example, it is asserted that housing animals in un-enriched environments that fail to satisfy their needs when enriched environments are known to be beneficial to them is unacceptable and should not be allowed.

2. *Procedures that some respondents consider unacceptable because of the degree of harm they cause to animals, regardless of the purpose of the work:*

Commonly cited examples include:

- use of non-human primates in procedures of substantial severity;
- genetic modification of primates and their use in research;
- use of non-human primates generally;
- use of companion animals;
- substantial severity procedures;
- any procedure that involves death as an end-point; and
- more radically, any experiment that involves more than mild suffering.

Maternal deprivation and learned helplessness studies were also mentioned in this context, but the Home Office says that neither would be licensed nowadays in Britain because the costs to animals could not be justified[6]. Procedures involving surgery on animals without anaesthesia were also mentioned - presumably because of misunderstanding Section 10 (2A). These would not be licensed, since local or general anaesthesia must

[6] Although maternal deprivation studies (like those of Harlow and colleagues in the 1960s and 70s) would not be licensed, maternal separation studies in which the young are temporarily separated from their mothers, might be licensed, provided the Home Office is convinced of the justification.

be provided for all surgical procedures - except for very minor procedures, where anaesthesia would be more traumatic to the animal than the procedure itself (see footnote 5, p. 54).

3. *Scientific purposes that some respondents perceive as morally unacceptable reasons for harming animals:*

Commonly cited examples include:

Modification of animals in:

- research aimed at shaping animals to fit into environments which are unacceptable or not optimal for the species in question;
- research aimed at 'improving' agricultural traits e.g. productivity.

Development and testing of certain classes of product, for example:

- household products;
- other non-medical products (e.g. agricultural and industrial products);
- 'lifestyle' or 'cosmetic' drugs (e.g. for slimming, smoking and hair loss through aging);
- generic or me-too drugs.

Other purposes:

- all defence research (not just offensive weapons research) e.g. research to counter and treat the effects of chemical or biological agents and conventional weapons (i.e. ballistic) wounding experiments;
- studies of the effects of tobacco and alcohol, and recreational drugs;
- a moratorium on xenotransplantation research;
- cloning research, especially cloning non-human primates;
- psychological experiments;
- fundamental research, particularly that involving non-human primates.

4.6.4 Practical ways forward

The constraints on animal use written into the Act are not particularly radical measures: most (with the exception of use of living animals in primary and secondary education) were in place under the Cruelty to Animals Act 1876 and/or are requirements of European legislation[7]. In practice, most of the further administrative restrictions implemented by the present government can be viewed as pushing on doors that were already open. For example, Great Apes have not been used in Britain for around 30 years; and cosmetics companies were already in a position to stop testing finished products and ingredients on animals (in Britain at least) when the present bans were announced.

In contrast, however, implementation of most, but perhaps not all, of the suggested candidates for further restrictions listed in 4.6.3 would be much more contentious. As the summary in 4.6.2 illustrates, it is clear that the general arguments surrounding the desirability of further constraints under the Act are complex and there is unlikely to be widespread consensus in many of the particular cases listed in 4.6.3. Nevertheless, in the context of the moral arguments outlined in Chapter 2, it is important that constant efforts should be made to diminish the moral tensions inherent in laboratory animal use, and not simply to rest with the *status quo*. We have identified a number of practical steps that we believe should be taken in order to clarify the position in certain cases, move thinking on in others, and, generally, help to ensure that strenuous and concerted efforts are made to work towards change in areas of concern.

Making existing limits explicit

Guidance on the operation of the Act (Home Office 2000c) advises that "the Secretary of State must be satisfied that protocols incorporate best practice".

[7] But note that the EU Directive covers fewer scientific uses of animals compared with the Act: for example, it does not cover education and training.

The Chief Inspector reports that "in some instances, there are national limits [on how animals can be used under the Act] which reflect best practice". These national limits include administrative and policy controls that are not explicitly stated in the legislation, such as the ban on cosmetics testing, and policies regulating the use non-human primates. Two examples of national limits are given in the note by the Chief Inspector: re-use of animals beyond the minimum requirements of the Act, and the use of "agreed 'minimal severity' protocols" for several procedures (Home Office 1998a).

However, published Home Office guidance on good practice and associated limits on uses of animals under the Act is rather limited. Supplementary guidelines are available on best practice for:

- generation and maintenance of genetically modified animals;
- microsurgical training schemes;
- antibody production;
- use of neuromuscular blocking agents; and
- conduct of regulatory toxicology and safety evaluation studies.

The supplementary guidelines contain examples of "minimal severity protocols" for these procedures. Beyond these particular areas of work, it is unclear what the "national limits which reflect best practice" actually are.

We believe that the Home Office, from its unique, comprehensive knowledge of how animals *actually* are used and its role in developing judgements on best practice, could play a more active part in informing licensees of current thinking within the Inspectorate on good practice. This is also important in providing more comprehensive information about how the cost-benefit assessment is applied in practice. The Chief Inspector's note on Consistency in the Inspectorate describes a range of guidance documents and databases that could be used to supply such information (Home Office 1998b).

For example, it would be helpful to provide explanation in the case of techniques and procedures that are generally agreed to be questionable but which may be licensed in certain particular circumstances. As an illustration, we understand that the current position in each of the three examples cited in 4.6.3 is as follows:

(i) Retro-orbital bleeding should be avoided where possible, because of the damage it can cause to animals' eyes – which is compounded by the difficulty of carrying out the procedure skilfully. The technique is mainly considered justifiable in pharmacokinetic studies, in which it is argued that it can be difficult to obtain sufficient blood volumes for analysis by other methods; must only be carried out under general anaesthesia and by skilled operators who are trained and experienced and can take blood by this route with only rare damage to the animals' eyes. Repeated sampling (at suitable intervals) is permitted, but animals with permanent eye damage must be humanely killed.

(ii) Tube restraint of rodents is nowadays licensed only for nose-only inhalation studies, in which, we understand, it is difficult to imagine an alternative method of restraint that could restrict the inhalation route sufficiently.

(iii) Use of ether as an anaesthetic is not licensed nowadays (for safety as well as animal welfare reasons), but ether is sometimes used as an irritant that can assist infection in studies where infection is by inhalation.

This kind of information should be available in the public domain.

On this point, several of the respondents who suggest further restrictions also observe that it is difficult for them to comment constructively in this

area, because they do not have access to detailed information about the full range of purposes for which animals are currently used, nor the kinds of techniques which are licensed. If informed consensus is to be achieved on such matters, it seems axiomatic that information should be provided to enable those both within and outside the animal-using scientific community to make informed comment and arrive at properly informed judgements. This question relates to more general procedural issues in cost-benefit assessment including questions of transparency and openness, and is considered in Chapter 5 of this report.

4.6.5 A *priori* restrictions cf. targets

Finished household product testing: a possible area for further advance restriction?

The use of animals in finished household product testing is one area of animal use in which a restriction might be considered to fall into the 'pushing at an open door' category noted above. Nowadays, few, if any, finished household products are tested in Britain, and the major companies, at least, say that they are now in a position where they rarely, if ever, need to use animals to test finished household products. There are no regulatory requirements to test such products except, in certain definable cases, under the new EU Biocidal Products Directive, and risk assessments are usually made using knowledge of the toxicity of the products' ingredients and their synergistic effects, enabling proper classification and labelling of the products under regulations administered by the Department of Trades and Industry (Boyd Group 2002b). The situation regarding household product testing appears to be similar to that pertaining when testing finished cosmetics products using animals was formally banned in 1997. In the case of finished household product testing, the Boyd Group (which includes a wide diversity of perspectives and expertise) has recently completed a detailed analysis of the possibility that tests on finished household products could be banned (Boyd Group 2002b).

Our view is that whilst a ban on the use of animals in testing finished household products would serve as a statement of moral principle, and could signal a potential point of no return, it would, like most of the current administrative restrictions under the Act, serve to formalise a largely already existing limit on animal use, and would therefore have little effect on the numbers of animals used for scientific purposes in Britain, nor on animal welfare in practice. There are also difficulties in providing an adequate definition of "household product" to enable proper implementation of such a ban, and to avoid tests simply being re-classified into other areas of animal use.

Other means of effecting change under the Act

As already noted, the arguments surrounding most of the suggestions for further administrative restrictions listed in 4.6.3 are complex and it will be difficult to gain sufficient agreement that there should be constraints in most of the areas suggested. However, imposing bans is not the only means of effecting change. We suggest that negotiating targets for change would be a more effective strategy for setting down moral markers under the Act. We have already alluded to this possibility in our analysis of moral arguments in Chapter 2, sections 2.4 and 2.5. Setting more general targets that could be worked towards alongside the usual case-by-case cost-benefit assessments, could help to move thinking on, and avoid inertia in the application of the Act. As part of the process of negotiation, areas of animal use that are currently considered problematic should be subject to detailed review.

Negotiating targets that could benefit animal welfare (not merely reducing numbers)

The idea of setting targets for overall reductions in animal use has been the subject of much discussion in the past. However, we believe that setting targets for reduction in overall *numbers* of animals used is not helpful. For example, it would be difficult to ensure that the reductions were

apportioned fairly, taking into account diverse needs in different areas of science, and that work did not simply move abroad. Targets for simple reductions in numbers, moreover, do not necessarily effectively address issues of animal suffering – for example, a reduction in number of animals used could in fact be achieved at the expense of causing more suffering to the fewer remaining animals. Similarly, it is important that optimal, not merely minimal, numbers of animals are used in any given experiment, so that animals are not wasted by being used in statistically invalid studies. Sometimes, achieving statistical validity will involve using more, not fewer animals.

For these reasons, we do not envisage that targets be set for overall reduction in the numbers of animals used. Rather, we recommend negotiation of targets for implementation of best practice and, where possible, for phasing out procedures that generate concern over the level of suffering they cause.

There should already be widespread consensus that animal procedures involving methods that have been superseded by refined techniques should not be allowed under the Act, and that the same principle should apply to standards of husbandry and care. In such cases, one might envisage that targets could be agreed by the scientific community itself to phase out use of the methods within a short timeframe. Targets might similarly be negotiated and implemented in other areas, such as reducing suffering in the use of non-human primates in research and testing.

Home Office statistics (Home Office 2002) show that the number of animals used in commercial concerns has declined year-on-year for the past 14 years and that this sector has reduced its overall use of animals by more than fifty per cent since 1987[8]. In part, this change has been achieved because senior management within industry views the reduction of animal use as a pressing goal that can bring indirect benefits for business, as well as direct benefits for animal welfare and often for science. There has been no similar reduction in use of animals in academia. This is partly because of the nature of academic, compared with commercial, uses of animals. Although there is, of course, considerable overlap in approach, the latter involves much more use of standardised tests, particularly those for toxicity and efficacy, that are repeated many times on different compounds and in different companies. An innovation that reduces the use of animals in even one such test could, potentially, have a dramatic impact on overall animal use within the commercial sector. In particular, the development and use of high-throughput *in vitro* screens during the initial stages of drug discovery has avoided the use of large numbers of animals in the pharmaceutical industry. Nevertheless, the difference in progress might also reflect a difference in management priority and pressure for change.

As we have noted, whilst reducing animal numbers is an important goal, there is also a need to reduce the suffering caused to the animals that are used. That is, to make progress in refinement of animal use – hence our recommendation above. At present, however, it is difficult to assess and monitor progress in refinement, because the Home Office statistics do not enable levels of animal suffering to be compared in the same way as numbers. As we have argued in 4.5.2, a new system of recording the severity of animal procedures is needed to assist in assessing progress in reducing in animal suffering.

Reviewing in detail areas that are considered problematic

Of course, people differ in their response to areas of animal use that some identify as being of

[8] This is on the basis of a reduction in the number of procedures: each separate use of one animal counts as one separate procedure (Home Office 2002).

particular concern. Given the diverse perspectives involved, it is likely that in many of the areas suggested in 4.6.3 it will be as difficult to negotiate consensus on realistic targets as it would be to gain agreement on outright bans.

Our view is that the APC, which brings a wide diversity of perspectives to bear, should investigate these more problematic areas of concern (such as procedures involving death as an end-point, fundamental and substantial severity research on non-human primates, and cost-benefit considerations in testing different kinds of product), with a view towards making recommendations on targets. The APC could:

(i) commission or carry out more detailed research in such areas, in order to probe the reasons for these uses of animals and the prospects for and barriers to further implementation of the Three Rs; and/or
(ii) review relevant project licence applications.

On the latter point, an APC working group has identified that the applications currently routinely referred to the APC are not necessarily the most significant, either in terms of welfare implications or wider trends, and that the Committee's expertise and limited time may be better brought to bear on applications which raise novel or controversial ethical, medical or scientific trends and issues. The working group has not yet finalised its report to the APC but has suggested that the Home Office should seek to identify applications which raise novel and problematic trends and issues and should refer them to the APC; and that the Home Office should publicise this change of approach, and invite the public to participate in identifying such trends and issues. Once the APC has agreed to the working group's report, a copy will be placed on the APC website (www.apc.gov.uk). (See Ch. 5: 5.2.3 for more on this review).

4.7 General conclusions

In this Chapter, we have examined the costs to animals and benefits that should be taken into account in the cost-benefit assessments required under Section 5(4) of the Act. We have collated lists of factors that are important in assessing costs and potential benefits of scientific work involving animals, have explored the definition of a 'cost', and have commented on areas that are currently perceived as problematic. In particular, we have made recommendations for widening the definition of 'cost' to be taken into account in the assessment, and for improving the system of assigning severity limits and bands in project licences.

We have also considered whether there should be any further absolute restriction (ban) on the nature or purpose of animal use permitted under the Act and have concluded that implementing further bans may not be the most appropriate means of progressing change in animal use. Rather, we believe that negotiating and setting targets for implementation of best practice and for phasing out procedures that generate concern over the level of suffering they cause would help in moving thinking on and avoiding inertia in the application of the Act. As part of this process of negotiation, we conclude that the APC should investigate the more problematic areas of concern, by commissioning or carrying out detailed research and/or reviewing relevant project licence applications. It may also have a role, with the Home Office, in facilitating meetings of relevant stakeholders to consider key issues and the possibilities for change.

We note that in assessing costs and benefits (as well as scientific validity) contestable judgements are involved. The quality of these judgements depends in large part on the diligence of those who make them, and also on their understanding and awareness of the issues. Thus it is critically important how these judgements are applied. In the next Chapter, we examine how cost-benefit

assessments are, and should be, approached in practice, and make recommendations that relate to the *process* by which the various judgements are made.

4.8 References

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CHAPTER 5

PRACTICAL PROCEDURES FOR COST-BENEFIT ASSESSMENT

5.1 Introduction

Section 5(4) of the Act requires not only that the harms (costs) to animals and benefits of particular projects be identified and assessed, but also that they be weighed one against the other. As noted in Chapter 4, the Home Office (2000a) interprets this as demanding that, for each project, throughout its duration:

(i) "the benefit is likely to exceed the welfare costs"; and
(ii) benefits are maximised, and costs in terms of animal use and suffering are minimised.

In our consultation document (at Annex A), we invited people involved in cost-benefit assessment at all levels, from those funding and/or regulating the work to those carrying it out, to inform us of "good practice with regard to the evaluation of costs and benefits and of judgements made in weighing these". We hoped to learn how those involved, including ERPs, ensure that "decisions in this area are fully and carefully considered in the light of relevant concerns and are furthermore, transparent and open in setting out the path which has been followed in reaching them".

The responses to the consultation offer very little general advice on how to weigh the harms and benefits of projects together in order to arrive at judgements about whether the benefits of projects are, as the Home Office puts it, "likely to exceed" their welfare costs to animals. This is not surprising. In Chapter 2, we pointed out that the application of cost-benefit assessments to animal research and testing cannot be quantitative or formulaic and, furthermore, can be contested on a number of general points of principle (2.4). Moreover, that such assessments are not the only grounds on which the acceptability of animal experiments is, nor should be, decided (2.4, also Ch. 4: 4.7).

Because contestable judgements are involved in deciding the acceptability, or otherwise, of animal experiments, articulation of the reasons for them is all the more important. Wider confidence in the judgements is likely to depend on how open and transparent they are, particularly with respect to the factors and interests that are taken into account. We have already explored in some detail the criteria that are appropriately taken into account - in our Chapters on the identification of costs and benefits (Ch. 4) and scientific validity (Ch. 3). However, as several respondents point out, what really matters is how conscientiously the various assessments outlined in these chapters are applied in practice:

"Whilst there can be guidelines on how to make such a judgement, it is how these are actually applied to each application that is crucial" (NAVS); "it is less important to expand the [cost-benefit] criteria than to introduce a national education and training plan ... in their application"(Anon.).

In short, **it is vital that the** *process* **by which cost-benefit assessment is carried out in practice is as rigorous, comprehensive and open as possible.**

Here, we consider a number of important questions and issues relating to this process, which were raised in both the responses and our deliberations. In particular, we highlight practical steps that can be taken to enhance confidence in the judgements that are made, and, we hope, help to ensure that best use is made of the time and effort put into the process. The issues include:

(i) the roles and responsibilities of the different people and bodies involved;
(ii) the importance of interim and retrospective review;
(iii) needs for information to facilitate cost-benefit assessments, including means of ensuring that the assessments are as sensitive as possible to all the different factors and interests involved; and
(iv) how openness and transparency in the process might be enhanced, and what information should be provided more widely.

5.2 Roles of the different people and processes involved in cost-benefit assessments

A number of different people and processes are currently involved in cost-benefit assessments of animal research projects. These include researchers themselves, the Home Office Inspectorate, the APC, and local ethical review processes (ERPs), which include Named People within establishments (Named Animal Care and Welfare Officers, NACWO; and Named Veterinary Surgeons, NVS), and funding bodies, as well as others such as editorial boards of journals.

This diversity of opportunities for cost-benefit assessment of laboratory animal use could, potentially, lead to duplication in the present system. Some respondents argue that this is the case where assessments of scientific validity are concerned. Our view is that each of the different processes approaches the cost-benefit assessment from a different perspective and that there need not be unnecessary duplication - but that there is a need for clarification of the roles and value of the various processes and improvements in communications between them.

5.2.1 Researchers

It is important to realise that researchers themselves bear responsibility for carrying out cost-benefit assessments of their work, including critical evaluation of the need for animal studies at all. While there are several different people and processes that are and should be involved in cost-benefit assessment under the Act, researchers are responsible for considering the ethics of their own work, throughout the whole life of the projects in which they are involved – from concept to completion and publication, dissemination and where possible application of the findings. The roles of the other processes, 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.

Applicants for project licences and holders of project licences already in force are responsible for the planning, design, execution and analysis of studies involving animals, and they must take steps to ensure that, at all times, likely benefits are maximised and harms to animals are minimised, and to satisfy themselves that the likelihood of significant benefit is always sufficient, given the harms.

Personal licensees who carry out work under particular project licences also play a vital role in cost-benefit assessment of on-going studies. Personal licensees (who may or may not also be project licence holders) have day-to-day contact with the animals involved in the studies and so are aware of cost-benefit considerations 'on-the-ground', so to speak, and can alert the project licence holder to any concerns they may have.

Potential project licence holders must communicate their cost-benefit assessments to local ERPs and then to the Home Office Inspectorate, using the Home Office application form and sometimes also supporting documentation, such as a lay summary for the ERP. ERPs also often require written interim reports to enable on-going cost-benefit assessment. Not only must researchers carry out their own cost-benefit assessments, but they must also explain these in an accessible manner, so as to enable informed consideration by others involved in the review.

It is important that the information provided by

researchers really addresses costs and benefits in an accessible and meaningful manner, and clearly communicates the researchers' own assessments of the balance of likely benefit over harm. Practical means of ensuring that this is the case are explored in 5.4.3, below. In particular, **we recommend that the project licence application form be designed so as to encourage more adequate, easy-to-understand and pertinent descriptions of costs and benefits and the relations between the two.** This is similar to the recommendation of the House of Lords Select Committee on Animals in Scientific Procedures that "Urgent consideration should be given by the Home Office to the simplification of project licences…". However, we do not agree that this simplification can be achieved by merely reducing the length of the licence application to 10 pages, as the Select Committee further recommended (House of Lords Select Committee on Animals in Scientific Procedures 2002).

5.2.2 Home Office Inspectorate

The Home Office is the final arbiter in cost-benefit assessment of licence applications. Technically, Home Office inspectors only *advise* the Secretary of State whether or not to license the work; but, in practice, the Home Office Minister acts on the advice of the Home Office inspectors, and in effect devolves responsibility for cost-benefit assessment to them.

The Home Office should be able to act as adjudicator of the applicants' own cost-benefit assessments. However, the descriptions of costs and benefits are separated in the project licence application form and the cost-benefit assessment itself is lost within the complexity of the form. In consequence, as things stand, the Home Office has in effect to 'make the case' on behalf of the applicant. Given the length and detail of the current project licence application form, it is astonishing that this weighing is not more directly and explicitly addressed. As noted above, **we believe that there is room for considerable simplification of the licence application form, and associated guidance notes, whilst at the same time providing more useful information about the applicant's own weighing of costs and benefits, and we consider this further in 5.4.3 below.**

Respondents to our consultation ask about the process by which the Home Office arrives at cost-benefit assessments. The criteria employed in the assessments, as described in Home Office guidance, have been listed in Chapters 3 and 4, but there is room for more transparency in the process by which these criteria are put together to arrive at judgements. See sections 5.4 and 5.5 below. Respondents also ask about the expertise that the Home Office employs in assessing scientific validity, likely benefits and implementation of best practice in animal use under the Act. At least one commentator suggests that the Home Office should make more use of independent panels of experts that the Home Office can draw on as required. In this context, the Chief Inspector comments that inspectors have considerable experience of research and/or clinical practice, still devote in the order of ten per cent of their time to continued professional development to keep abreast of advances, and do not work in isolation - there is considerable internal referral of cases, use of literature and other databases, and no shortage of scientific and regulatory contacts who can advise (formally or informally) on contemporary thinking or the specifics of applications. In addition, applications are forwarded to external assessors as and when required.

5.2.3 Animal Procedures Committee

In addition to requiring review of licence applications by the Home Office Inspectorate, Section 9(1) of the Act permits the Secretary of State to consult "an independent assessor or the Animal Procedures Committee" before granting a licence. By convention, the following classes of

application are automatically referred to the APC:

- those involving the use of tobacco and tobacco products on conscious animals;
- microsurgical training;
- the use of non-human primates in procedures of substantial severity;
- the use of wild-caught, non-human primates;
- the testing of cosmetics (no longer authorised in the UK).

In the last three years the APC has advised on several applications in the first three of those categories, but none in the last two. The current process adopted by the APC in evaluating most applications is as follows:

- A working group considers the application, which may include seeking further information from the applicant, and makes written comments. While the costs and benefits are considered, the APC are unable to perform a full cost-benefit assessment as they do not have all of the necessary information available to them. This is unlike the Home Office or the Inspectorate who have a more intimate knowledge of all aspects of the proposed procedure, such as the researchers themselves, the facilities and the standards of care.
- The APC receives the application and the comments of the working group.
- The APC discusses the application at its meeting and talks directly with the applicant and/or inspector to answer any outstanding questions, if necessary.
- A recommendation to the Home Office is made. If it is to allow the application, the Committee sometimes suggests that extra conditions be imposed. It can also ask to be kept informed of developments.

We are currently reviewing our role in considering licence applications (as noted in Ch. 4: 4.6.5). At the time of writing, this review had not yet been completed, but we have already concluded that the APC's deliberations can add value to an application by:

- *Adding expert comment and reflection,* since the APC is an expert committee, which in view of its scientific, medical, animal welfare and veterinary expertise can give an informed view on particular issues. However, because of the complexity and wide range of modern scientific research the APC cannot always give such an expert view, and in such cases informed specialist advice might be more appropriately obtained by the Home Office's use of other independent assessors.
- *Adding an independent element to a review of an application,* since the APC forms an independent part of the licensing system. It follows that even if we do not suggest any amendments to the licence (and often we do) we have added appreciable value, as Ministers and the public can be reassured that a project proposal has been assessed by a committee which is independent of the normal licensing process.
- *Concentrating minds,* since it is probable that the prospect that a particular class of application will be examined by the APC will concentrate the minds of applicants more than might otherwise be the case, and may thus ensure a better application, for example, in terms of consideration of the Three Rs.

However, in our ongoing review we have also concluded that the list in 5.2.3 does not necessarily identify the most significant applications, either in terms of welfare implications and wider trends in animal use. We have noted that it is vital that applications which raise novel or controversial ethical, medical or scientific trends and issues are subject to thorough independent/external scrutiny in advance – and, rather than routinely considering particular classes of application, we might make a more helpful contribution by advising on applications that raise such novel or problematic trends and issues, particularly if there was public

participation in identifying particular areas of concern.

5.2.4 Funding bodies

Scientific peer review of applications to external funding bodies to support projects involving animals focuses mainly on quality of science issues and the likely benefits of research, though peer review guidelines sometimes include rather general questions about proposed uses of animals.

A number of scientific respondents emphasise the importance of funding body review in critically evaluating researchers' assessments of scientific validity of proposals to use animals, as well as the need to carry out the research at all. Several respondents suggest that, when such work has been successfully peer reviewed in competition for limited funds from a mainstream funding body, there is little need for further challenge of the researchers' own assessments of the scientific validity and/or necessity of the work. However, other respondents express concern about the quality of such scientific peer review, particularly in terms of whether and how far it includes critical evaluation of the scientific validity of animal studies, along the lines shown in Box 2 in Chapter 3. For example, a body representing over 30,000 academic biomedical researchers in the UK (and so which should have sound experience of peer review) recommends that "funding bodies should address questions of animal use more directly within their peer review processes". And the RSPCA asks, "How often do the peer review panels of research funding bodies sit back and really think creatively about whether there is an alternative approach to the problem?"

It is clear that the level of detail of ethical review of animal use varies between funding bodies. Also, that there are subtle, but important differences in emphasis and approach between funding body peer review and evaluation by the Home Office and ERP of researchers' cost-benefit assessments. In particular, it is important to note that, under the Act, assessment of scientific validity and necessity of research is approached in relation to the harms that are likely to be caused to the animals, whereas funding body and commercial sponsors' reviews tend to focus more on the science itself and whether the work will offer value for money. Whilst ethical implications for animal use and application of the Three Rs are considered by funding bodies, they are not the central concern, and are not considered in the detail involved in review by Home Office and ERP. Moreover, because scientists involved in the studies, including regulators and peer reviewers, are close to the particular area of work, they "are likely to have a mind-set predetermined by their experience of research carried out on specific animal models" (RSPCA) and may not always challenge the need for particular animal procedures as critically as a more independent reviewer. This is discussed further in the next section.

5.2.5 Local Ethical Review Processes

Local Ethical Review Processes appraise researchers' cost-benefit assessments with particular regard to local factors, and can play a vital role in ensuring that there is continuous, on-going review of harms and benefits and widespread awareness of possibilities for implementation of the Three Rs within establishments. In these respects, especially, the ERP offers advantages that it would be difficult to achieve in the other processes outlined above.

In relation to these functions, however, the name "ethical review process" could be taken to imply that ethical evaluation of applications takes place solely, or mainly, when the ERP examines the application. This detracts attention from the researchers' primary, continuing, responsibility for considering the ethics of his or her own work. Furthermore, the major strength of the ERP is that it can provide advice to researchers in relation to local factors, with ethics *per se* being but one part of this advice. For example, the ERP can advise on whether and how far the local facilities available for carrying out the work will meet the needs of the

science and enable the best possible animal welfare.

Examples of approaches that can help to ensure that local ethical review processes provide useful, high quality, advice for researchers, and so help to achieve tangible benefits for both animal welfare and science, include:

- involving a wide variety of well informed people in the review process, who each bring their particular expertise to bear on the issues, including:
  - Named persons (the NVS and NACWOs), who can advise, for example, on practical means of improving animal care and use and implementing refinements;
  - people with statistical expertise;
  - scientists outside the particular field of work under consideration, lay people and people outside the establishment - all of whom can bring a 'fresh eye' to the issues raised by the work;
- ensuring that review and advice on cost-benefit assessment and related issues is not seen solely in terms of the particular project concerned, but is also used to identify and provide advice on issues that have a wider bearing on animal use within the establishment;
- setting up means of disseminating information about the Three Rs and related issues to researchers - e.g. internal web-sites - and helping to ensure that NVS, NACWO and animal technicians' concerns and advice are communicated to researchers, for example;
- putting in place procedures for training that aim to ensure that everyone involved with the use of animals (both researchers and animal care staff) receives on-going support, advice and opportunities for professional development, particularly with respect to local (in-house) factors. This should involve more than simply sending licensees away on one-off training courses;
- ensuring that retrospective/interim review is used to assist researchers in re-evaluating their own cost-benefit assessments, and in refining on-going work, as well as informing other local reviews, and is not merely a paper exercise (see also 5.3 below).

See also advice from the Chief Home Office Inspector (Home Office 2000b).

Note, however, that the ERP's role is not 'merely' advisory - local review processes can also play a more decisive role in that they can advise the establishment's Certificate Holder (whom the ERP 'belongs to' and who bears ultimate responsibility for all work carried out within the establishment) not to support an application to carry out animal work.

The work of ERPs, particularly their role in enhancing communication about animal use within establishments, can be assisted by requiring researchers to prepare project licence applications that clearly explain the researchers' own cost-benefit assessments. We have made recommendations in this regard in sections 5.2.2 and 5.2.3 above, and 5.5.1 and 5.5.2 below.

Regarding advice on scientific validity, in particular, several of the scientific societies that represent researchers argue that ERPs should have little or no role in assessments of scientific validity when these have already been performed as part of peer review for funding. In cases where projects have not been subjected to peer review, however, "the [ERP] can include further expert scientific advice" (Anon.). See also 5.2.4, above. The implication of this argument is that the ERP lacks the expertise to contribute on matters relating to scientific validity, and in any case would simply duplicate efforts made elsewhere. In this context it is notable that the report of the recent Home Office review of the ERP includes a comment that:
"Some [scientists] still seem unwilling to allow

their science to be challenged within the ERP, and are sometimes reluctant to offer a sustainable justification of proposed work" (Home Office 2001a, para. 34).

Our view is that consideration of certain aspects of scientific validity by local ERPs could offer a number of important advantages that are unlikely to be realised in funding body or other peer review processes. We have already observed that the focus of funding body review tends to be on the quality of the science *per se*, and rather less on the necessity to use the particular animal-based methods. ERPs can consider the scientific validity of animal experiments with respect to *local* factors, and so are in a strong position to provide advice on how the particular personnel, facilities and other resources available might affect the scientific validity of the work. They include input from Named people who can provide up-to-date, expert advice on veterinary matters that can affect scientific validity - such as methods of anaesthesia and analgesia; as well as from the NACWO(s), who can offer advice on methods of animal care and husbandry, which might affect the science. Moreover, it is important to recognise that the ERP includes peer scientists from within, and sometimes outside, the establishment, who can make informed comment on scientific aspects of applications and on-going work. (Just as the term *ethical* review process should not be taken to imply that consideration of 'the ethics' is restricted to this one place, it should not be taken to imply that the ERP cannot 'do science'.) In addition, ERPs sometimes include expert statisticians and information scientists who can also provide relevant specialist advice. In these respects, in particular, the ERP's work can 'add value' to the assessment of scientific validity, and the advice given to researchers, rather than simply duplicating effort.

5.2.6 Publication

Publication, or other means of communicating the methods and results of animal studies, opens work to widespread peer review. Along with other means of retrospective review, this process can be very valuable in informing future cost-benefit assessments. For further discussion, see 5.3, below.

5.2.7 Relationship between the various processes involved in cost-benefit assessment of applications

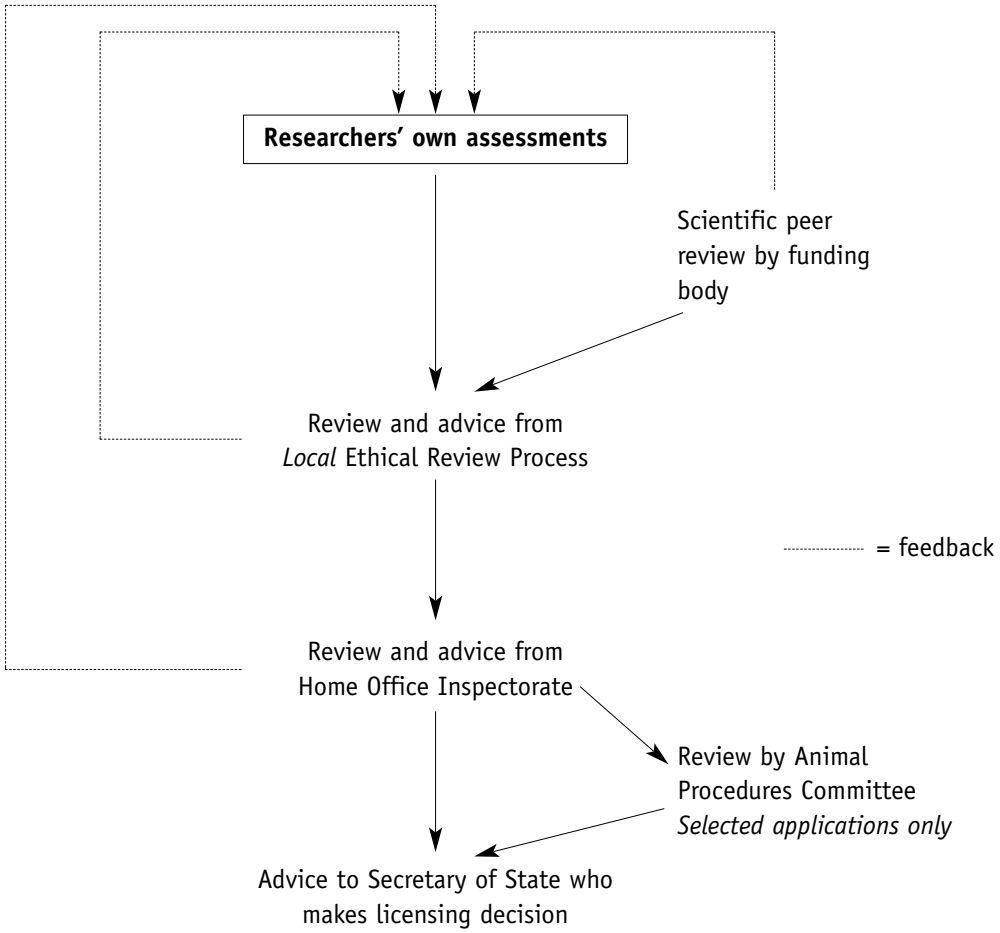
The relationship between the different processes involved in cost-benefit assessments of project licence applications under the Act are summarised in the Figure below. As noted, primary, on-going responsibility for cost-benefit assessment of projects involving animals lies with the researchers who plan and carry out the studies. Funding body peer review also contributes to the assessments by providing advice and adjudication on certain aspects, particularly quality of science, when decisions are made whether or not to support the work. Ethical review processes within establishments bring a range of local knowledge and expertise to bear in evaluating the researchers' assessments and providing advice to assist them in minimising harms and maximising the benefits of their animal studies. Home Office inspectors evaluate the cost-benefit assessments provided in licence applications and decide whether or not to advise that the Secretary of State grants the licences. Some classes of application are routinely referred by the Home Office to the APC (as discussed in 5.2.3), which similarly advises the Secretary of State. Roles and responsibilities for on-going and retrospective review are considered in 5.3, below.

Home Office, ERP and funding body review each offer valuable and distinct independent perspectives on researchers' own cost-benefit assessments, and it is important that this variety and independence remains. There can also be an important role for the APC. When the Committee advises Ministers about an application, we believe we have the potential to provide an informed, thorough and critical scrutiny, which can complement the expert advice provided to Ministers by the Inspectorate.

The diversity of different reviews also brings opportunities for each to learn from, and inform, the others – but in practice, communication between the different processes is limited. It is important that the various processes are able to seek information from one another, wherever this would be of value in informing their own deliberations and in avoiding duplication of effort. For example, the outcomes of funding body review can be valuable in informing both ERP and Home Office review of researchers' cost-benefit assessments. Similarly, information from the ERP's review and adjudication could be helpful in informing the Home Office of any particular local issues and concerns.

5.3 On-going cost-benefit assessment of work in

Figure: Relationship between the different people and processes involved in cost-benefit assessment of project licence applications



progress

As noted in Chapter 4, Home Office guidance emphasises that cost-benefit assessment should not be a one-off event, occurring only at the licensing stage of the project, but an on-going process, continuing throughout the life of the project. Researchers themselves bear responsibility for ensuring that this is the case. All involved should constantly be alert to the harms and benefits resulting from the work, and take steps to minimise harms, maximise benefits and critically evaluate the need for the studies in light of the actual harms caused to the animals.

The Home Office regards local ERPs as having a key role in facilitating and assisting researchers' on-going application of the cost-benefit assessment. This function can be fulfilled in particular through the ERP's roles in facilitating communication between animal care staff and scientists, disseminating information in order to enhance researchers' awareness of opportunities for implementing the Three Rs, providing a forum for on-going consideration of ethical aspects of projects and advice to licensees - as well as more formal retrospective and interim review.

On the last point, Home Office guidance on the operation of ERPs requires that they carry out "retrospective reviews" of projects, but gives no further advice on what this should entail or what it should achieve (Home Office 2000b). Our view is that formal, ERP-driven opportunities for both interim review of work in progress and retrospective review of completed studies can have important advantages. Interim review helps licensees, in particular, to re-assess approaches in light of new information about the Three Rs and developments in technique, and to implement current guidance on good practice. Both interim and retrospective review can also provide feedback to licensees and ERPs that can assist them in approaching cost-benefit assessments of on-going work, as well as any future applications.

Our enquiries reveal that current practice in interim review by ERPs usually includes (at least):

- reviewing the use made of the licence;
- assisting researchers in re-evaluating the initial cost-benefit assessment in light of experience and identifying scope for further application of the Three Rs;
- identifying any training needs for personnel, or needs for other support and advising accordingly; and
- identifying any problems that have not yet been dealt with, and advising on possible solutions.

The Home Office appears to devolve responsibility for routine interim review to ERPs, but the results of these reviews are not formally communicated to the Home Office. In our view, the Home Office Inspectorate should take note of the findings of interim review by ERPs - if only to assess the value of the efforts put into them, and perhaps to inform their own cost-benefit assessments in future.

Funding bodies also have a role to play in on-going cost-benefit assessment. It is important that funding bodes who are on record as being committed to the Three Rs should make proper financial provision to enable application of new refinements during the life of their grant-supported projects.

Publication of the results of animal studies throws the work open to wider ethical scrutiny. This kind of retrospective review, which can involve public participation as well as scientific peers, can potentially play a part in informing and shaping future cost-benefit judgements. However, to achieve any such benefit, it is vital that the animal procedures are reported in sufficient detail to allow others to follow, and criticise, the methods accurately; that advances in application of the Three Rs are documented and highlighted using searchable key words; and that the objectives of the studies are clearly expressed.

5.4 Needs for information to assist in cost-benefit assessment under the Act

5.4.1 Information about the factors that should be taken into account

It has already been noted that the quality of cost-benefit assessments under the Act largely depends on the approach of those who make them, and in particular whether they are responsive to all the relevant factors and interests involved (Ch. 4: 4.1 *et seq*.; see also the report of a working party of the Institute of Medical Ethics - Smith and Boyd 1991). Indeed, being clear about the full range of factors that should be considered is not only important in the context of weighing harms and benefits in order to arrive at judgements, but also in devising and implementing strategies for minimising harms and maximising benefits. If, for example, costs to animals are to be minimised, all the different factors that can constitute and contribute to those costs must first be *recognised*.

We have already observed that Home Office guidance on the factors to be taken into account in cost-benefit assessment is spread across several different documents, each of which has been produced for a different purpose. The notes to applicants for project licences (Home Office 2001b) offer the most comprehensive advice, but are not particularly user-friendly. **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 ethical review under the Act, such as members of ERPs (see Ch. 3: 3.5).**

Based on the responses to our consultation, Home Office advice and other published schemes, we have drawn up lists of factors that are important in cost-benefit assessment, and these are presented in Chapters 3 and 4. These are first attempts. **We recommend that Home Office should produce, or commission production of, a comprehensive list of factors, perhaps as a guidance document that could be made available on the web.**

Such a list should not be viewed as a static document, fixed for all time, but as a 'work in progress' that will evolve in light of experience. It is also vital that any such scheme is used to develop approaches to cost-benefit assessment that are best suited to the particular circumstances involved - that is, it should guide thinking, and should *not* become mechanical, box-ticking exercises that merely adds to bureaucracy.

5.4.2 Case studies to inform practice

Several respondents to our consultation feel that the process by which the Home Office arrives at judgements about the balance of benefit over harm is too opaque, and a variety of organisations suggest that case studies to illustrate how the cost-benefit assessment is carried out in particular circumstances would be very helpful.

The provision of illustrative case studies would certainly be consonant with the general approach that is both described and advocated in this report. Such examples could help to inform debate on how the cost-benefit assessment is actually applied; could assist researchers in preparing applications, as well as others such as members of ERPs, in providing advice and carrying out reviews – and might help to enhance wider confidence in the judgements that are made under the Act (see also 5.5 below).

We believe that the Home Office could play a more active part in informing licensees of current thinking within the Inspectorate on good practice. In our report on openness (Home Office 2001c), we recommended that an annual report on the work of the Inspectorate be published. This could contain a review of significant and interesting judgements. Such a review need not be presented as a set of complete and detailed case studies, but in the form of a

commentary, drawing attention to pertinent points that raise general issues. This would bring advantages in that it would provide advice on current thinking and precedent (e.g. the conditions under which the use of retro-orbital bleeding could be approved), and would also relate to the question of consistency within the Inspectorate. More widely, such a review would help to make clear how judgement is actually exercised.

Other bodies involved in cost-benefit assessment might also publish such reviews. The APC already provides commentary on its review of certain classes of application, in its Annual Report. Presumably, ERPs could also provide this kind of commentary on cases and advice given.

5.4.3 Information and analysis in project licence applications

We have observed that the project licence application form, despite (or perhaps because of) its complexity, does not enable an accessible account of the weighing of harms and benefits to be presented (see 5.2.2 above); nor do we feel that it encourages applicants to identify costs and benefits clearly. Several respondents comment that the present application form is too complex. **Again, we emphasise that we believe that there is room for the licence application to be reviewed with the aim of making it more straight-forward, in order to assist applicants in providing more meaningful, easy-to-understand and pertinent descriptions of costs and benefits and accounts of their assessments of the relations between the two.**

In this context, we commend the kind of approach used by the Animal Health Trust, which is illustrated in Annex F. This simple model invites applicants to pin-point clearly the potential harms and benefits of their work, to list these concisely, and to provide explicit analysis of the weighing they have carried out. For example, such a format encourages descriptions of costs to animals that are not merely accounts of what will happen to the animals, but of what this will actually *mean* for the animals, in terms of the potential suffering or other harm they will experience - see also discussion in Chapter 4: 4.3.1.

Although there might be difficulties in adapting the current application form, **we recommend that the Home Office gives consideration to amendments along the lines suggested above.** We do not believe that this would necessarily add to the existing form; rather we believe that such changes may have the potential not only to enhance the quality of the information provided, but also to reduce the length and complexity of the form.

5.4.4 Scope of licences subject to cost-benefit assessment

We observe that the kind of approach illustrated in Annex F would not work for all current project licences. For example, it would be difficult to apply this format to large licences that cover a wide range of different kinds of study, united by a general theme; or which license certain tests that can be carried out in a variety of different circumstances. Indeed, we find it implausible that careful and detailed cost-benefit assessment, of the kind required under the Act, can be carried out in the case of applications for such wide ranging licences. In such cases, there may be a lack of information about the specific contexts in which work will be done and, as a consequence, about the particular harms and benefits likely to result. To deal with this difficulty, some establishments have put in place procedures to ensure that advice on reducing harms and maximising benefits (and, where necessary, ethical adjudication on the balance of benefit over harm) can be provided whenever significant new work is started under such licences.

Where wide-ranging licences are concerned, there may be insufficient information available at the application and licensing stages to enable informed cost-benefit assessment and pertinent

advice to be given concerning actual uses of animals. For this reason, the appropriateness of such licences should be reviewed.

5.5 Enhancing openness and transparency in cost-benefit assessment

Perhaps the main concern about procedures for cost-benefit assessment, expressed largely, but not exclusively, by those critical of animal use under the Act, is the degree of openness and transparency in licensing decisions:

"... the cost:benefit test, which has to reflect current public mores, simply cannot work properly without transparency. If we continue to have secrecy, its operation will continue to reflect the aspirations and values of researchers and industry, not those of the wider public" (BUAV).

In this context, we believe that the pursuit of transparency is not about forcing disclosure of matters that have been kept secret, but of revealing matters that have remained obscure. From this starting position, we have identified several strategies that should help to improve confidence in the implementation of the Act. These include:

- making the factors that are taken into account more explicit and providing examples of their application, in order to promote greater openness about the reasons for the judgements that are made (see 5.4.1, above);
- widening opportunities for consultation and comment on cost-benefit assessments under the Act; and

providing more meaningful information about what actually happens to the animals used.

5.5.1 Widening consultation on cost-benefit assessments under the Act

The establishment of local ERPs has been an important step in widening consultation on cost-benefit assessments under the Act, because ERPs include a diversity of scientific perspectives, provide for input from animal care and veterinary staff, and, in many cases, also involve lay participants, who have no direct interest or involvement in animal experiments, and/or participants who come from outside the establishment.

We believe that lay (or 'non-technical') participation in the ERP brings considerable advantages, particularly when at least one such participant comes from outside the establishment. It has been suggested that external and lay participation can promote transparency in ethical review, because the role can be compared with that of a non-executive director, who has to satisfy him/herself that the process is rigorous and that all the members are playing their proper parts and thus help to ensure integrity of the *process* of review. However, we believe that the main value of involving lay and/or external people lies, not in engendering wider trust in the process itself, but in raising questions that those who are closer to the work may not have considered. This is because such participants can provide an independent, novel perspective on the issues involved, bringing a 'fresh eye' that might result in challenge of accepted norms of custom and practice (see Smith and Jennings 2002 for further discussion). This conclusion is supported by the recent Home Office review of the ERP (Home Office 2001a), the report of which comments that:

"Lay members of ERPs have asked questions from a different perspective. They have constructively challenged existing assumptions and practices, with the result that improvements have been made with respect to licence applications and animal care and use" (Home Office 2001a).

To facilitate such wider involvement in cost-benefit assessment under the Act, there are needs for clear, non-technical accounts of the costs and benefits of projects presented for prospective or on-going review by the ERP. Again, we commend the

kind of approach illustrated in Annex F. See also 5.5.2, below.

Another means of widening consultation, as NAVS suggests, would be:

to make "pending" licence applications "available for public inspection (names of researchers and institutions need not be detailed) for a certain time period. Any interested individuals could offer informed opinions. The licence would only be approved providing that there is no relevant opposition offered within the set time period."

Our view is that this would add too much to the already large bureaucratic burdens of the licence application process. As in many other regulatory areas there has to be a practical limit on the degree of public participation in judgements involved in implementing the legislation. It is, however, important that the procedures used to arrive at the judgements are perceived as trustworthy and that opportunities are provided for wider comment on the judgements that are made. To help to achieve these aims there is a need for greater publication of information about licences and work in progress, to enable more widespread, informed comment and criticism and, with this, provide an opportunity to influence future assessments (see below).

5.5.2 Publication of information about licences and animal use under the Act

The underlying principle of the Freedom of Information Act 2000 is that information will be disclosed unless an exemption is argued for in specific cases - such as where personal safety or academic or commercial interests would be prejudiced by disclosure. Section 24 of the Act makes it an offence for anybody to disclose information about animal procedures received in confidence under the terms of the Act, except in order to discharge their functions under the Act. Our 2001 report on Openness (Home Office 2001c) recommended that Section 24 be repealed or relaxed as a necessary step towards greater openness, and concluded that there should be no blanket exemptions on the duty to disclose information. This was also raised by the House of Lords Select Committee on the Use of Animals in Scientific Procedures (House of Lords Select Committee on Animals in Scientific Procedures 2002). The Government has now established a working group to consider Section 24.

The Home Office, like other public authorities, is also required to develop a publication scheme, in order to publish information proactively. **Our report on Openness recommended that this should include summaries of project licences, which are comprehensive and detailed enough to provide the reader with a clear indication of the costs and benefits of the project – and to this we would add an account of why the licensee(s) judge that the likely benefits exceed the likely costs.**

Our 2001 report on Openness also recommended that the usefulness of the information in the annual Home Office *Statistics of Scientific Procedures on Living Animals* should be improved, and that this should include "providing fuller details of the severity of experiments", in order to "assist the public to come to an informed view". We have already noted that the information on severity currently provided in the Home Office statistics is limited to overall severity bands of projects, which do not accurately reflect the harms actually caused to animals used under the Act (Ch. 4: 4.5.2). It would be more appropriate to record information on severity at the protocol level, but it is unclear exactly how such a system would operate in practice. It is clear, however, that **a new system of recording the severity of the effects actually experienced by the animals is needed, that could be used to enhance the quality and usefulness of the public information provided in the Home Office statistics and also help to indicate progress made in refining animal use year-on-year.** This

ties in with a recommendation from the House of Lords Select Committee on Animals in Scientific Procedures that details of costs and benefits from anonymised project licence applications should be made public following confirmation of approval and funding (House of Lords Select Committee on Animals in Scientific Procedures 2002).

5.6 General conclusions

In this Chapter we have explored the roles and responsibilities of the different people and processes involved in cost-benefit assessment under the Act, and have 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.

Because contestable judgements are involved in cost-benefit assessments, it is vital that the process by which these assessments are carried out in practice is as rigorous, comprehensive and open as possible, and we have made recommendations on a number of practical steps that can be taken to enhance these aspects.

We have further emphasised that the need for cost-benefit assessment is not restricted to the licence application stage, but extends throughout the life of projects involving animals. Again, researchers themselves bear responsibility for ensuring that this is the case.

Many of our recommendations in this Chapter, and elsewhere in our report, highlight strategies that can help to ensure that cost-benefit assessment under the Act continues to evolve and that inertia in the application of the Act is avoided. This is the context in which we draw together a summary of our analysis, conclusions and recommendations, in the following, final, Chapter of this report.

5.7 References

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CHAPTER 6

SUMMARY AND CONCLUSIONS

6.1 The nature of cost-benefit judgements under the Act

Almost everyone involved in the debate on animal experiments, whatever their overall perspective, shares the belief that animal suffering, like human suffering, matters – and should be avoided wherever possible. Such a position calls on those who carry out, or require, animal experiments to engage in constant, critical evaluation of the need for and justification of using animals at all, and to undertake exhaustive efforts to minimise the suffering of the animals that are used and to maximise the value of the information gained from the studies.

It is in the nature of scientific experiments that outcomes are uncertain, so evaluation of costs to animals and likely benefits of studies can be based only on potential, likely and probable, not certain, outcomes. Cost-benefit assessment, moreover, is not morally neutral. For example, values come into play in deciding what should count as a 'legitimate' cost or benefit, and the relative weights the different kinds of costs and benefits should be accorded.

For these reasons, cost-benefit assessments under the Act must be regarded as judgements that are both contestable and interim, in that they should change over time – as new scientific information becomes available, understanding of animals and their welfare improves and refined or non-animal methods are found, for example – and also in response to changes in wider societal perspective. In short, cost-benefit assessment should be an evolving process.

Those who use, or require the use of, animals in experiments bear primary responsibility for ensuring that this is the case. Researchers and regulators, as well as others involved with the implementation of the Act, should not rest with the *status quo*, but should subject their cost-benefit judgements to on-going and detailed critical evaluation. This will involve engaging in creative and imaginative thinking, so as to identify strategies and targets that can avoid or reduce animal suffering, maximise the benefits of studies in which animals are used, and so help to diminish the moral conflicts that are inherent – and, most people believe, regrettable – in the use of animals in research.

Our analysis, and most of our recommendations, can be viewed in this light. We have not attempted to draw conclusions that can be regarded as settling, or drawing lines under the issues involved, but have highlighted areas in which we believe that more creative thinking is required and have identified steps that can be taken to encourage this. We intend our practical recommendations to serve as challenges towards imaginative – and, we hope, productive – thought by everyone involved, whatever their overall perspective on the issues.

We have examined and drawn conclusions regarding:

(i) the moral validity of animal experiments;
(ii) assessments of the scientific validity of animal experiments;
(iii) the factors that it is important to take into account in cost-benefit assessments under the Act;
(iv) some particular issues relating to the application of the assessments; and
(v) practical procedures for carrying out cost-benefit assessments.

We summarise our conclusions in each area below, bearing in mind the wider perspectives described above.

6.2 The moral validity of scientific experiments

In Chapter 2 we have indicated some important common ground upon which the Animals (Scientific Procedures) Act is premised. This lies chiefly in the widely shared belief that animal suffering cannot be viewed as a matter of moral indifference, and that critical evaluation and justification is called for. This fact also helps explain the character and structure of the Act, especially the important element of cost-benefit assessment, and the role of this assessment in fostering the appropriate sensitivities. In reflecting on the arguments for and against animal experimentation, we have found there to be morally defensible considerations adduced for a range of views. However, we have also detected ways of keeping up the momentum for change, both by distinguishing more sharply between arguments that deserve to be ignored and arguments that cannot be ignored, and by identifying areas of potential compromise and negotiation.

6.3 The scientific validity of animal experiments

Cost-benefit assessment under the Act operates on the assumption that animal experiments can, potentially, be scientifically valid. That is, that they are capable of giving results that are (i) relevant to their purpose and (ii) reliable, in that they are reproducible within and between laboratories and over time. If animal experiments are not, or as is sometimes claimed, can never be scientifically valid in these terms, the cost-benefit assessment becomes redundant, because there will be no potential benefits to weigh against the harms and the use of animals cannot be justified.

We emphasise that an absolute, categorical position that *all* animal experiments are scientifically invalid is untenable. However, so too is the opposite categorical position, that the validity of using animals in experiments is a forgone conclusion and should not be questioned. The case that animal experiments can produce scientifically valid results is clear, strong and sustainable, but cannot be construed as an absolute case that every potential use of animals is scientifically valid and fail safe. Nor, moreover, does the case that valid extrapolations can be made from animal experiments necessarily imply that the use of animals is the only or best means of achieving the particular objectives.

These conclusions highlight the general point that, whilst scientific validity is a condition capable of being fulfilled, it has to be judged case-by-case and subjected to detailed, critical evaluation. This will involve evaluating whether and how far the proposed use of animals is the most appropriate approach - including whether it is appropriate to use animals at all - and whether and how far it is reliable and relevant to the objectives or questions being asked.

In order to ensure that such assessments continue to evolve, individuals and establishments should consider whether and how far they engage in sufficient innovative, creative, flexible and challenging thinking when choosing methods and models to address scientific research or testing questions.

Regarding the use of animals in toxicity testing, we conclude that there are needs for more efforts to assess the value of such tests in predicting effects in humans – particularly since the results of an animal test are almost invariably used as the benchmark against which the validity of an alternative, non-animal test is assessed.

Moreover, we observe that there is an element of circularity in arguments about where responsibility for the scientific appropriateness of animal tests carried out for regulatory purposes actually lies, which is difficult to break. We emphasise that regulatory authorities do have a role in cost-benefit assessment of animal procedures, and need to allow scientists flexibility of approach to ensure that only the most valid and vital animal tests are carried

out. By the same token, toxicologists have a duty to continue critically to evaluate the appropriateness of the animal tests they perform and to raise questions and concerns with the regulators.

Regarding experimental design and analysis of results, we observe that surveys of published papers sometimes reveal basic errors in study design, which reduce or obviate the scientific validity of the animal studies. We emphasise that researchers must be aware of the value of good experimental design and planning (such as choice of appropriate models) and implementation. They must also be aware of the importance of statistical input in their experimental designs, understand what can be achieved with wise statistical consideration, and know where to go for advice.

In this context, we recommend that each establishment should ensure that a statistical service is available to its licensees (establishments might collaborate in providing such a service). We also conclude that it is important to evaluate the success of the statistical component of Module 5 in imparting general statistical skills and understanding. The education and training sub-committee of the APC will be asked to consider this matter further and make appropriate recommendations.

6.4 Factors to be taken into account in cost-benefit assessment under the Act

We have observed that cost-benefit assessment involves contestable judgements. It follows that the quality of cost-benefit assessments under the Act, including assessments of scientific validity, largely depends on the approach of those who make them, and in particular whether and how far they can show that they have been responsive to all the relevant factors and interests involved. Moreover, if costs to animals are to be minimised and likely benefits maximised, all the different factors that can constitute and contribute to those costs and benefits must first be recognised.

There is a need for an easy-to-use, comprehensive list of factors to be taken into account in assessing costs, benefits, and also scientific validity, that can guide researchers and others engaged in ethical review under the Act, such as members of ERPs. Based on the responses to our consultation, Home Office advice and other published schemes, we have drawn up lists of factors that are important in cost-benefit assessment, and these are presented in Boxes 2 and 3 in Chapter 3 and Boxes 4 to 7 in Chapter 4 of this report. For other examples of such lists see Smith and Jennings (2003). These are first attempts. We recommend that the Home Office should produce, or commission production of, a comprehensive list of factors, perhaps as a guidance document that could be made available on the web.

In order to avoid inertia in the application of cost-benefit analysis under the Act, it is important that these criteria evolve with experience, and should and will be informed by retrospective review. It is also vital that any such scheme is used to develop approaches to cost-benefit assessment that are best suited to the particular circumstances involved – that is, the criteria should guide thinking.

6.5 Some particular issues in the application of cost-benefit assessments

In line with our general philosophy that cost-benefit assessment under the Act should be an evolutionary process, we have explored some of the more difficult areas in the application of such assessments. We have used these difficulties to illustrate the depth and comprehensiveness of the analyses required in cost-benefit assessment, offering brief descriptions of the issues as we see them, but not necessarily attempting to prescribe solutions or make recommendations.

6.5.1 General recommendations to assist in 'moving thinking on'

From this analysis, and in the context of the moral arguments described in Chapter 2, we have identified a number of practical steps that we believe should be taken in order to avoid inertia in

the application of the Act and, generally, help to ensure that strenuous and concerted efforts are made to work towards change in areas of concern.

In particular:

(a) We recommend negotiation of targets for implementation of best practice and, where possible, for phasing out procedures that generate concern over the level of suffering they cause. Responsibility for identifying and pursuing such targets should lie primarily with the scientific community itself. For example, there should already be widespread consensus that animal procedures involving methods that have been superseded by refined techniques should not be allowed under the Act, and that the same principle should apply to standards of husbandry and care. In such cases, one might envisage that targets could be agreed by the scientific community itself to phase out use of the methods within a short timeframe. Targets might similarly be negotiated and implemented in other areas, such as reducing suffering in the use of non-human primates in research and testing. We have stressed that whilst this is first of all the responsibility of the researchers, there may also be a role for the APC together with the Home Office to facilitate meetings of relevant stakeholders to consider key issues and the potential for change.

(b) In addition to this challenge to the scientific community, we also recommend that the APC, in dialogue with informed public opinion, should investigate the more problematic areas of concern, such as procedures involving death as an end-point, fundamental and substantial severity research on non-human primates, and cost-benefit considerations in testing different kinds of products, with a view towards making recommendations on targets. We could:

  (i) commission or carry out more detailed research in such areas, in order to probe the reasons for these uses of animals and the prospects for and barriers to further implementation of the Three Rs; and/or

  (ii) review relevant project licence applications.

On the latter point, our applications working group has recently suggested that the Home Office, separately or in conjunction with the APC, should seek to identify applications which raise novel and/or problematic trends and issues and should refer them to the APC. Furthermore, that the Home Office should publicise this change of approach, and invite the public to participate in identifying such trends and issues.

(c) In order to facilitate public involvement in identifying areas of concern, and to assist licensees, the Home Office should provide more information on current thinking within the Inspectorate regarding 'good practice', drawing on the Home Office Inspectorate's unique, comprehensive knowledge of how animals *actually* are used.

In addition to these general recommendations, we have also drawn conclusions that advocate or suggest particular actions in some of the more problematic areas. These are indicated below:

6.5.2 Definition and description of costs to animals

It is important to recognise that a description of the 'costs' of a study should not be simply a description of what will happen to the animals, but of what this will actually mean for the animals in practice. This should encompass social and psychological costs, such as fear, anxiety, loss of memory, confusion, and boredom, as well as more overt physical harms. It is also important to consider the particular needs of the particular animals involved, and to be sensitive to the likely effects of experiments on the individuals used.

In addition, more explicit recognition within project licences of costs due to capture, confinement, transport, husbandry systems and general handling

should help to ensure that strategies are put in place to minimise their adverse effects on animals. As part of this, costs due to transport of all species covered by the Act should be included in cost-benefit assessments under the Act. Currently, only the adverse effects of transport of non-human primates are required to be considered as part of the assessment of costs, yet prolonged transport is also a problem for other animals such as genetically modified mice which have often been developed in and therefore must be transported from mainland Europe or the United States, or even further afield.

6.5.3 Assigning severity limits and bands

A number of difficulties are inherent in the classification of severity of protocols and projects currently used by the Home Office. Some of these difficulties arise because different people have different understandings of, views on, and perceptions and interpretations of, the terms suffering, severity, mild, moderate, and substantial. Others are a consequence of the different ways in which severity limits and bands are used in practice. In particular:

A variety of procedures that, to many commentators, seem to have the potential to cause substantial suffering are classified as moderate. In order to distinguish more clearly the wide range of levels of severity that is encompassed by the term 'moderate', we recommend that this category of severity be sub-divided.

We conclude that overall severity bands are inadequate both for purposes of cost-benefit assessment and providing public information about severity. On these grounds, we doubt the value of assigning overall severity bands for projects, and invite the Home Office to consider reviewing the utility and effectiveness of severity banding for assessing, monitoring and managing projects. Furthermore, we believe a new or revised system should be put in place for public information purposes.

It would also be very helpful if there was more material to illustrate how the severity classification system operates in practice. In particular, we recommend publication of:

- more examples to illustrate what counts as mild, moderate and substantial severity than currently appears in the Home Office guidance on the Act, so as to enable wider understanding of what each category actually means for the animals that experience it; and
- information about how the limits and bands are interpreted, assessed and used by people working under the Act and by the Home Office.

As we have argued in other areas, thinking on the issue of severity should continue to evolve. In particular, the criteria used to define the levels of severity should be regularly reviewed in the light of increasing understanding of the nature of animal suffering, and such publications updated accordingly.

6.5.4 Duplication of animal studies

Genuine duplication of animal studies, without strong and sustainable scientific justification, is unacceptable and should not take place. In both industry and academia, researchers who propose and/or carry out animal work bear responsibility for avoiding unnecessary duplication of animal use, and need to employ considerable determination and imagination to ensure that animals are used *only* when sufficient useful and relevant data are unavailable.

In the case of duplication as a result of commercial confidentiality, we welcome work on the new UK Interdepartmental Concordat on Data Sharing, but it is too early to say how effective this will be in preventing unnecessary duplication of animal studies. The impact of the Concordat on Data Sharing should be monitored carefully and reports placed in the public domain. If the Concordat does not prove to be effective, more binding measures, such as legislation, will be needed to achieve the Concordat's aims.

6.6 Practical procedures for cost-benefit assessment

As we have already argued, because contestable judgements are involved, it is vital that the process by which cost-benefit assessment is carried out in practice is as rigorous, comprehensive and open as possible, and encourages creative and imaginative thinking.

6.6.1 Researchers' responsibilities and the project licence application form

We emphasise that researchers bear responsibility for carrying out cost-benefit assessments of their work, including taking steps to minimise harms, maximise benefits and critically evaluate the need for animal studies at all. However, we observe that the actual weighing of costs and benefits is not built into the project licence application form and that the Home Office has, in effect, to make the case on behalf of the applicant. Given the complexity of the current application form, it is astonishing that this weighing is not more directly and explicitly addressed.

We recommend that the project licence application form be modified in order to encourage and assist applicants in thinking through their cost-benefit assessments, and enabling them to provide more adequate, easy-to-understand and pertinent descriptions of costs and benefits and accounts of their assessments of the relations between the two. We do not propose adding to the existing form; rather, we believe that such modification has the potential not only to enhance the quality of the information provided, but also to reduce the complexity and possibly the length of the form.

6.6.2 Other review processes

In addition to researchers themselves and the Home Office, we note that the APC, funding bodies, local ethical review processes (ERPs), and others, such as editorial boards of journals engage in cost-benefit assessment of laboratory animal use. We argue that, rather than duplicating effort, each of these processes brings valuable and different perspectives to bear, that can help to ensure that researchers' cost-benefit assessments are subject to critical evaluation, and advice provided, at all stages in animal research and testing – from the germ of an idea, to publication of the results of the studies, and beyond.

6.6.3 Scope of licences subjected to cost-benefit assessment

We find it implausible that careful and detailed cost-benefit assessment, of the kind required under the Act, can be carried out in the case of large licences that cover a wide range of different kinds of study, united by a general theme; or which license certain tests that can be carried out in a variety of different circumstances. Where such wide-ranging licences are concerned, there may be insufficient information available at the application and licensing stages to enable informed cost-benefit assessment and pertinent advice to be given concerning actual uses of animals. For this reason, the appropriateness of such licences should be reviewed.

6.6.4 Cost-benefit assessment as a continuous process

Cost-benefit assessment should not be a one-off event, occurring only at the licensing stage of the project, but an on-going process, continuing throughout the life of the project. Those responsible for designing and conducting experiments themselves again bear responsibility for ensuring that this is the case.

Formal, ERP-driven, opportunities for both interim review of work in progress and retrospective review of completed studies can assist researchers in, for example, re-assessing approaches in light of new information about the Three Rs and developments in technique, and implementing current guidance on good practice. Both interim and retrospective review can also provide feedback to licensees and ERPs that can assist them in approaching cost-benefit

assessments of on-going work and future applications. Although the Home Office appears to devolve responsibility for routine interim reviews to ERPs, the Home Office Inspectorate should take heed of the findings of these reviews – if only to assess the value of the efforts put into them, and perhaps to inform their own cost-benefit assessments in future.

We emphasise that funding bodies also have a role to play in on-going cost-benefit assessment. In particular, it is important that funding bodes who are on record as being committed to the Three Rs should make proper financial provision to enable application of new refinements during the life of their grant-supported projects.

6.6.5 Enhancing transparency in cost-benefit assessments under the Act

It is vital not only that cost-benefit assessments are as rigorous, comprehensive and forward-thinking as possible, but also that they are seen to be so. In this context, we believe that the pursuit of transparency is not about forcing disclosure of matters that have been kept secret, but of revealing matters that have remained obscure. From this starting position, we have identified several strategies that should help to enhance openness in the implementation of the Act.

We have commented on the need to make the factors that are taken into account in the assessments more explicit. Other strategies that can aid transparency include:

- providing case material to illustrate how such factors are actually applied in cost-benefit assessment, in order to promote greater openness about the reasons for the judgements that are made;
- widening involvement in cost-benefit assessments under the Act; and, to support this:
- providing more meaningful information about work that is licensed, and what actually happens to the animals used.

Case material to illustrate the reasons for the judgements that are made

In our report on Openness, we recommended that an annual report on the work of the Inspectorate be published. In order to provide advice on current thinking and precedent, and to help make clear how judgement is actually exercised in cost-benefit assessment, we further recommend that this annual report should contain a commentary on significant and interesting judgements. Such a review need not be presented as a set of complete and detailed case studies, but in the form of a commentary, drawing attention to pertinent points that raise general issues.

Widening involvement in cost-benefit assessment

We believe that lay (or 'non-technical') participation in the ERP brings considerable advantages, particularly when at least one such participant comes from outside the establishment. Whilst the involvement of lay and/or external people can assist in engendering wider trust in the process itself, in our view the main benefit arises because such people can raise questions that those who are closer to the work may not have considered. To facilitate such wider involvement, there are needs for clear, non-technical accounts of the costs and benefits of projects presented for prospective or on-going review by the ERP (see also 6.5.1 above).

Providing more meaningful information about licences and severity

It is also important that opportunities are provided for wider comment on the judgements that are made. In particular, there are needs for more information about the kind of work that is licensed, and the severity of its effects on animals.

In our report on Openness we recommended that the Home Office publication scheme under the Freedom of Information Act should include summaries of project licences, which are comprehensive and detailed enough to provide the reader with a clear indication of the costs and benefits of the project – and to this we would now

add an account of why the licensee(s) judge that the likely benefits "exceed" the likely costs.

Finally, it is clear that a new system of recording the severity of the effects actually experienced by the animals is needed, that could be used to enhance the quality and usefulness of the public information provided in the Home Office statistics on animal use and also help to indicate progress made in refining animal use year-on-year.

ANNEX A

THE COMMITTEE'S CONSULTATION LETTER ON THE REVIEW OF COST-BENEFIT ASSESSMENT UNDER ASPA

PROCEDURES COMMITTEE
ROOM 978, 50 QUEEN ANNE'S GATE
LONDON SW1 9AT
Tel: 020 7273 2915 or 2770
apc.secretariat@homeoffice.gsi.gov.uk

6 December 2000

Dear Reader

CONSULTATION PAPER ON THE COST/BENEFIT ASSESSMENT AND THE ANIMALS (SCIENTIFIC PROCEDURES) ACT 1986

Introduction

1. This letter seeks your views on the cost/benefit assessment used in the consideration of applications to carry out animal experiments under the Animals (Scientific Procedures) Act 1986.

2. The role of the Animal Procedures Committee (APC) is to provide the Home Secretary with advice, independent from the Home Office and its Inspectorate, about the legislation and his functions under it. Our membership consists of experts from a wide variety of backgrounds. By law, we must take account of both the legitimate requirements of science and industry and the protection of animals against avoidable suffering and unnecessary use in scientific procedures.

3. We have previously undertaken an overall review of the Animals (Scientific Procedures) Act 1986, the conclusions of which appear in our annual report for 1997. As that report explains, we received during the course of the review a large number of comments about the cost-benefit assessment. These comments showed that many believe that the cost-benefit assessment has made a contribution to animal welfare since the 1986 Act first brought it into law, but that some thought that the law was not applied with sufficient rigour. More generally there was some uncertainty about how the cost/benefit assessment operates in practice - uncertainty, regarding the factors that are taken into account and how these are put together in coming to a judgement. We concluded then that we should "produce and publish an extended statement on the assessment of costs and benefits required by the Act". We hoped that this would make an important contribution to the effective operation and public understanding of the principles and functioning of this significant piece of legislation. This consultation document is our first step towards doing that.

4. Section 5(1) of the Act describes a project licence as a licence granted by the Secretary of State specifying a programme of work and authorising the application, as part of that programme, of specified regulated procedures to animals of specified descriptions at a specified place or places. Section 5(3) of the Act states

that a project licence shall not be granted unless the Secretary of State is satisfied that it is undertaken for one or more of the following 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 in primary or secondary schools;
- Forensic enquiries;
- The breeding of animals for experimental or other scientific use.

Section 5(4) of the Act provides that "in determining whether and on what basis 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". The Committee intends to offer the Government its considered advice on the assessment of adverse effects and benefits, and in particular hopes to be able to offer views on how to ensure that the assessment is sensitive to all relevant considerations, accords them proper significance, and is as transparent and open as possible.

5. We are seeking views chiefly on three areas of concern: the scientific validity of experimentation on animals; the identification and weighing of harms and benefits; and the development of good practice and processes in carrying out the Cost/Benefit assessment.

The scientific validity of Animal Experiments

6. A(SP)A 1986 requires the Home Secretary to weigh the likely adverse effects on animals of the programme of work, against the benefits likely to accrue. Those people, however, who believe that animal experiments are scientifically invalid (i.e. are scientifically misleading, yielding no worthwhile or reliable knowledge) consider that this assessment is very straightforward. They would argue that experiments on animals yield no benefits and therefore no licences should be granted.

7. Clearly, the argument regarding the validity of animal experiments is integral to any review of the cost-benefit assessment. Those at either end of the spectrum of views on this issue argue about 'validity' as if it were an all or nothing affair. The arguments used to support these opposing positions focus on the specific failures or successes of animal experiments and then extrapolate to a general position – animal experiments as a whole are either invalid or valid science. A question in the debate is whether or not animals provide a good model for humans based on their physical and physiological similarities and differences[1]. However, animals are used for many different purposes, and to obtain many different types of information which is subsequently used in a variety of ways. They are not used only as models of humans. The research goals can be study of the animals themselves, or the acquisition of general biological knowledge. Basing the validity argument solely on the relevance of animal models to humans therefore seems unsustainable.

[1] An annex to this letter provides a discussion of such similarities and differences in the heart and blood of humans and animals.

8. A more considered review of the issue of validity in relation to the cost-benefit assessment seems necessary which would need to take into account at least:

- the purpose and experimental design of the research/testing programme;
- the reasons for believing the animal model will give insight into a problem;
- what the individual experiments are designed to achieve;
- the potential and/or limitations of other approaches;
- how the results will be used; and
- the benefit of fortuitous discovery.

9. We would welcome your views on the following two questions:

- *Can the validity of experiments on animals be argued in absolute terms as set out in paragraph 7 or should this be considered on a case by case basis taking into account the factors such as those in para 8 above? It would be helpful if you could explain the criteria you believe should be used to assess the scientific validity of animal experiments.*
- *Do you consider that the cost-benefit assessment adequately addresses the scientific validity of projects and individual experiments within these? Who do you consider has/should have responsibility for assessing validity (e.g. the researcher, the funding body, the Animal Scientific Procedures Inspectorate, Ethical Review Process, regulators, other)?*

The Identification and Weighing Of Harms And Benefits

10. Section 5(4) of the Animals (Scientific Procedures) Act 1986 requires that "in determining whether and on what basis 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".

11. The way costs and benefits are currently determined by the HO Inspectorate, together with a guide to how decisions are made with respect to the weighing of these – the justification of each project - is set out in Chapter 2 Annex 1 of the review of ASPA contained in the APC report for 1997.

12. The ASPA also sets out in Section 5(3) the broad purposes for which animals can be used (see paragraph 4). In recent years, the Secretary of State has introduced restrictions on work for which licence authorities can be obtained. There are some types of animal experiment - to test offensive weapons, alcohol, cosmetics and tobacco products, and use of some species (the Great Apes) - which the Home Office has ruled out in principle, on the grounds that the Government considers the costs are unjustified, or alternatives are available or they are "morally objectionable". The number of licensed procedures involving the use of genetically modified animals is increasing, and there may be costs and benefits specific to this expanding area that should be given separate consideration. We would therefore be grateful for your views on these issues.

13. The APC would welcome views on the following questions:

- *Are there additional categories of uses of animals, or particular types of procedure, which should be viewed as unacceptable either in terms of the level of suffering involved or the species of animal that is used regardless of the benefit that comes from such use or procedures?*

- *Are there some types of benefit (the overall purpose of the experiment) that might be held as not justifying the use of animals or justifying it only in exceptional circumstances regardless of whether or not the animals would suffer?*
- *Are all relevant harms and benefits identified by current HO practice? Even if, by its nature, the weighing of costs and benefits always has to be a matter of opinion, is there need for further clarification of the criteria which have been or should be employed in particular cases?*
- *Are costs other than those involved in, or consequent upon, the actual procedures given their due weight? These include the physical and psychological harms/sufferings associated with capture, confinement, transportation, social isolation, husbandry systems and general handling of animals. Should death in itself be considered a harm and what weight should be given to this in the cost-benefit assessment?*
- *Are there costs to animals, for example, aspects of poor welfare or undesirable changes in animals, which could be specific to transgenic animals or animals treated with products from genetically modified organisms? Do you consider that any of these costs could never be justified by benefits?*
- *Please give detailed examples of benefits specific to the use of transgenic animals, or to the treatment of animals with products from genetically modified organisms, which are likely to be very great. Are there, or will there be, benefits whose magnitude is too small, or whose likelihood of accruing is too remote or too distant in time, to outweigh the costs?*

14. Research is increasingly a multinational process and UK researchers often collaborate with scientists abroad who are operating under different regulatory regimes which may have much less regard for animals and their welfare.

- *Do you believe that this is a significant problem? If so, what might be done to address it?*

The Development Of Good Practice And Processes In Carrying Out The Cost/Benefit Assessment

15. We are aware that there is experience of assessing and weighing adverse effects and benefits outside the sphere of animal experimentation from which we might be able to learn. Comparisons analogous to the one which is at the centre of ASPA have a part in the work of the HSE for example, and also the Environment Agency. Similarly, those considering the acceptability of clinical trials in human subjects have to make careful appraisals of the likely adverse effects and the likely benefits. The APC would welcome contributions regarding the questions in this paper from those involved in these fields.

16. We are keen to be informed of good practice with regard to the evaluation of costs and benefits, and of judgements made in weighing these, amongst researchers themselves and also in the work of the ethical review process. We hope to hear from those involved at all levels, from those funding and/or regulating the work to those carrying it out. We hope to learn how they ensure that decisions in this area are fully and carefully considered in the light of all relevant concerns, and are furthermore, transparent and open in setting out the path which has been followed in reaching them.

17. We are particularly keen to learn how ERPs are addressing the sort of questions set out in this paper. We will especially welcome submissions describing procedures aimed at ensuring thorough consideration and appraisal of the costs and benefits of experimental programmes, and of how judgements on their scientific and ethical justification are made.

Conclusion

18. Please let us have your comments by 28 February 2001. Reply to the postal address above or to **apc.secretariat@homeoffice.gsi.gov.uk**

19. I will of course be happy to deal with any queries you may have. We will, if asked, disclose the contents of responses to this letter and the identities of respondents. Please let us know if you would prefer us not to do either or both of these things in your case.

20. We have placed this letter on the APC's website at **http://www.apc.gov.uk**

RICHARD WEST
Secretary

ANNEX B

THE USE OF ANIMALS IN MEDICAL RESEARCH – AN EXAMPLE (ANNEX A TO CONSULTATION LETTER)

1. Whatever one thinks of the ethics and validity of animal experiments it is clear that some aspects of animals are at least similar to man. For instance the heart of all mammals is a pump that contains four chambers and the exit from each chamber has a valve. Blood is brought into the heart by veins and carried away by arteries. The pressure maintained by the heart in all mammals - man included - is about 100 mm mercury.

2. The hearts of other orders of animal are distinct. For example those of crabs only have one chamber. Therefore it appears more useful to use the heart of any mammal to model the heart of a human being as a pump than that of a crab. Some elements of particular mammals are more specialised than the same elements in man. For example the ears of rabbits are extremely efficient organs for temperature control whereas in man the ears do not have that function. Some elements of animal structure and function are more directly equivalent to those elements in human beings, while others are less directly equivalent.

3. There are fundamental similarities between all living things which are made up of cells. Each cell has a nucleus. A nucleus controls protein production, the cell is controlled by receptors on the surface and the cell releases agents into the surrounding environment. In order to understand whether the cell or tissue or organ is comparable in the structure or function between species, detailed analysis of the exact function and structure in both man and the lower species must be made. Each case must be judged on its own merits.

4. The biological structure and function of organisms is determined by genes within chromosomes in the nucleus of the cell. An analysis of the similarity or difference of genetic make up of two organisms gives us some idea whether an organism might be a more or less appropriate model for understanding the human structure and function. The gene determines particular aspects of the animal, for example the structure of a protein. A gene in one species can give rise to a protein which is exactly similar to that in another species. Even if that protein has a slightly different structure it may have the same function in the two species.

5. It can be said that in terms of their genes apes are 99% equivalent to human beings. Even a worm shares 36% of its genes with human beings. This implies that as long as the differences between animals and humans are understood they might give useful information about the structure and function of the human body. As one moves towards worms more care in extrapolation is required, but a recent study of the genome of the worm C. elegans has produced extensive information about how the genomes of all species might function.

6. An example of how the study of cells in different species of mammals might help understand disease in man is found in a study of the platelet. The platelet is a small cell that circulates in the blood whose job is to stop bleeding when an artery or a vein is punctured. Inappropriate activation of this system of stopping bleeding can lead to thrombosis of a vessel and its consequent occlusion. This leads to heart attack or stroke. As often in medicine one finds that an inappropriate activation of an important function (like stopping bleeding) leads to a human disease (like thrombosis). Platelet volume distribution is an important physiological parameter in that it is similar in all mammals from the mouse to man and

that it is unlike any other cellular volume distribution found in any cell in any species.

7. Animal studies have shown that larger platelets are more "sticky" and therefore more likely to produce thrombosis. This led to the finding that in men with heart attack the volume distribution curve is shifted to higher values. The understanding that the nature of the shift in the human platelet volume distribution curve can be analysed in animals brought about an advance in our understanding of the events that might precede a heart attack. The reiterative experimental process in animal experiments produced results that allowed new human experimentation to be performed. Those human experiments again gave rise to new animal experiments.

8. This process of reiteration between animals and man in understanding platelet physiology and pathophysiology was only possible because of the similarity on many parameters in the nature of platelets in all mammals.

ANNEX C

LIST OF RESPONDENTS TO COST-BENEFIT REVIEW CONSULTATION[1]

1. P James
2. H Jert
3. Professor Sir C Spedding
4. P Tatham
5. Dr N Salihbegovic
6. D Kelman
7. Mrs L Piddington
8. Mr R Leventon
9. Professor M J Reiss, Institute Of Education
10. A Murrell
11. University Of Birmingham
12. M Pearson
13. Dr S Handley
14. Mrs S Mackay
15. Mrs M Cameron
16. H Cullens
17. Secretary General Cioms, WHO
18. C Emery
19. Mr G Johnson
20. Mr J Smith
21. Dr J Guggenheim, Cardiff University
22. RSPCA Member
23. Dr P Riley, Institute Of Child Health
24. J & P Spencer
25. C Tyrell
26. Professor A Brown, Exeter University
27. Miss L Owen
28. Mrs E M Gray-Jones
29. Ms I Miller
30. Ms J Humphrey
31. Ms M Stoneham
32. Dr Graham Quintiles Ltd
33. Mrs B Hayman
34. Ms G Russell
35. Mrs T Yates
36. Ms L M Smith
37. Mr P R Bava
38. Ms P Burgees
39. G Girdwood
40. Mrs R Williams
41. Ms R Pawling
42. Mr G Hale
43. Ms P Black
44. Mr J Newcombe
45. Professor P Fox, Royal College Of Anaesthetics
46. Mr Lazenby & Ms Holloway
47. Ms L Williamson
48. British Association For Psychopharmacology
49. R Allen
50. B Pollack
51. Dr I D Bross
52. Womens Food And Farming Union
53. S G Luque
54. Mrs S Sindle
55. Professor P Vallance
56. Mrs E Stoneman
57. Miss E Poole
58. Mr A E Pavitt
59. M Curati
60. H Reeve
61. Ms E Eldridge
62. L Good
63. Friends Of The Animals International
64. H Price
65. Miss S Gosling
66. L Freston
67. Progressive Supranuclear Palsy
68. Muscular Dystrophy Campaign
69. Mrs P Corr
70. Mr M Lewicki
71. Ms S Smith
72. A Tyler, Animal Aid
73. The Physiological Society
74. Dr E Moore

[1] Only includes those respondents who did not ask to remain anonymous.

75. Ms C Lack
76. D Pullin
77. D Pageau
78. Nuffield Council On Bioethics
79. Professor R Douglas, City University
80. Dr L Harvey
81. Mr D Barnett
82. British Lung Foundation
83. A Nex
84. Mr L Gregory
85. Ms L Goldberg
86. Scottish Landowners Federation
87. Heriott-Watt University
88. Ms I Boyne
89. Dr R Hubrecht, Universities Federation for Animal Welfare
90. Medical Research Modernisation Committee
91. Dr P Sumariwalla
92. Mr T Mccann
93. The Royal College Of Physicians And Surgeons Of Glasgow
94. Mr A Careful
95. Research Into Ageing
96. B & K Universal Ltd
97. R C Fischera
98. National Anti-Vivisection Society
99. Ms G U Wolft
100. Mr & Mrs F Duffin
101. Mr S Hazelwood
102. Backcare
103. West Wales Animal Aid
104. Ms D Allchorne
105. Motor Neurone Disease Association
106. Dr J Lucke
107. University Of Bristol
108. Mr G N Williamson
109. Action Research
110. Catholic Centre For Animal Welfare
111. Epilepsy Research Foundation
112. Mr Y Wilson
113. Mrs M Pooley
114. M Campbell
115. Royal Ulster Agricultural Society
116. Dr R Ryder
117. Blond Mcindoe Centre
118. Mrs F Allan
119. Environment Agency
120. Miss L Georgiades
121. Ms Hayman
122. Mrs J Alexander
123. Mr J Brown
124.Church Of England Archbishops Council
125. Ms E Van Der Skeen
126. Ms M Smith
127. Mrs P Dibley
128. Humane Slaughter Association
129. Dr S Russell
130. Mrs A Duval
131. Dr J Nicholas
132. Mrs M Carit
133. University Of Bath
134. Mrs G Wallis
135. Mrs W Morley
136. Imperial College
137. Mr J Jacobs
138. Intervet
139. J Long
140. Mrs L Brown
141. Meningitis Research Foundation
142. Mr J Morgan
143. Mr T Macmanus
144. Ms A O'Connor
145. Moredun Research Institute
146. Mr P Dyer
147. Centre for Applied Microbiology and Research (CAMR)
148. Mr A Fitzgerald
149. Humane Research Trust
150. Ms C Heeley
151. Imperial Cancer Research Fund
152. Ms S Cannon
153. Inspire
154. Mr R Roach
155. National Kidney Research Council
156. National Heart Research Council
157. Anon
158. Association For Spina Bifida & Hydrocephalus
159. Croydon Animal Aid

160. Animal Health Trust
161. Ms K Perlo
162. Tayside R&D Consortium
163. Mr I Russell
164. Alex
165. Ms M Redgrave
166. Ms J Shortland
167. Hannah Research Institute
168. M Bard
169. Mrs C Evans
170. University Of St Andrews
171. Professor D Macnab
172. Professor Skehel
173. Ms K Buttebank
174. The Royal Society
175. K Sullivan
176. M Hatwell
177. L Richter
178. Europeans For Medical Advancement
179. Dr P Weinberg
180. D Evans
181. A Lyme
182. Pesticides Safety Directorate
183. Edinburgh University
184. University Of Sheffield
185. Association Of Veterinary Teachers And Research Workers
186. Institute For Animal Health
187. School Of Pharmacy
188. J Williams
189. S Hatton
190. A Symes
191. M Herbert
192. Mrs U Bates
193. Ms P Mullane
194. Mr A Tabrun
195. L Winter
196. E Edwards
197. R Williams
198. Miss D Ronen
199. Mr J Day
200. S Gould
201. D Stuart
202. Biomedix Holdings
203. Mrs S Clayton
204. Restoration of Appearance and Function Trust (RAFT)
205. Ms C Bridges
206. Ms D Marshall
207. Ms J Roxburgh
208. Ms M Harling
209. Mr J Marshall
210. Ms V Bell
211. Prof M Balls
212. Ms R Marshall
213. Doncaster Animal Protection Society
214. Mr R W Brown
215. Ms L Newcombe
216. Ms C Belkowska
217. Mrs P Kinnunen
218. Isle Of Wight Animal Preservation & Action Group
219. Ms S Blair
220. Dr J Gunn
221. Institute Of Food Research
222. University Of Durham
223. Ms J Ness
224. Scottish Agricultural College
225. Ms M Clay
226. UK Xenotransplantation Interim Authority (Ukxira)
227. G Lillywhite
228. Ms J Hardiham
229. Mr M Coulouis
230. Fund for the Replacement of Animals in Medical Experiments (FRAME)
231. British Society Of Animal Science
232. Macaulay Land Research Institute
233. T Conway-Grim
234. C Iles
235. Ataxia
236. National Asthma Campaign
237. Mr A Andrews
238. People for the Ethical Treatment of Animals (PETA)
239. University Of Paisley
240. Sanofi-Synthelabo
241. Wellcome Trust

242. Royal College Of Physicians Of Edinburgh
243. Association Of Medical Research Charities (AMRC)
244. Medical Research Council (MRC)
245. British Heart Foundation (BHF)
246. Academy Of Medical Sciences
247. Health & Safety Executive (HSE)
248. Dr C Clayton
249. Ms S Dickens
250. Scottish Association For Marine Science
251. N Ireland Against Animal Experiments
252. University Of Keele
253. Biomaths & Stats Scotland
254. Catholic Study Circle For Animal Welfare
255. D Maddocks
256. Animal Concern
257. M Pettet
258. R Edwards
259. Mrs J Pothecary
260. Mr P Sullivan
261. University Of Reading
262. Mr L Short
263. Mrs U Hiatt
264. University Of Sussex
265. Institute of Professionals, Managers and Specialists (IPMS)
266. Breakthrough Breast Cancer
267. Mr C Male
268. Institute Of Biomedical Science
269. King's College London
270. Biotechnology and Biological Sciences Research Council (BBSRC)
271. University Of Leicester
272. Mr H Turtle
273. Farm & Food Society
274. Ms M Munro
275. Mr C Pitt
276. Miss H Brand
277. Ms P Potts
278. Naturewatch
279. Nottingham Trent University
280. Ms C Adams
281. Mr C Sims
282. Mr K Richardson
283. Mrs C Cawthorne
284. The Royal Society Of Edinburgh
285. National Radiological Protection Board
286. Dr D Bruce Church Of Scotland
287. Dr D Miller
288. University Of Manchester
289. University Of Newcastle
290. University Of Glasgow
291. Dr Hadwen Trust
292. Research Defence Society
293. British Union for the Abolition of Vivisection (BUAV)
294. Royal College Of Obstetricians & Gynaecologists
295. The Boyd Group
296. Royal Society for the Prevention of Cruelty to Animals (RSPCA)
297. British Toxicology Society
298. Uncaged Campaigns
299. Advocates For Animals
300. University Of Liverpool
301. British Veterinary Association (BVA)
302. Cardinal O'Connor, Roman Catholic Church

ANNEX D

SCHEMES FOR THE ETHICAL REVIEW OF THE COSTS AND BENEFITS OF ANIMAL PROCEDURES[2]

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[2] This list is not exhaustive and only lists schemes that have been published.

ANNEX E

EXAMPLES WHERE THE USE OF GENETICALLY ALTERED ANIMAL MODELS HAS LED TO BENEFITS FOR HUMANS

These examples are taken from responses to the consultation letter, and have been anonymised.

- A genetically modified form of the cytokine interferon-B has been used successfully to limit the debilitating effects of multiple sclerosis in thousands of patients. In this case the compound had to be tested in primates since rodents have a different form of interferon-B and do not respond to the compound used to treat humans.
- The production by animals of genetically modified proteins to treat devastating human diseases has already been enormously beneficial (e.g. insulin, growth hormone). Large quantities of high quality hormones which are not contaminated (e.g. with prions, HIV) can be produced in this way. This is likely to provide safe treatments for many other human diseases in the near future. All will have to be tested on animals for their efficacy and safety.
- The use of antitrypsin, which is being extracted from the milk of a herd of transgenic sheep, as a possible treatment for cystic fibrosis and other lung disease. This is in the final stages of clinical trials.
- Many genetically modified mice have proven invaluable in the understanding of normal biological function and disease, and in the development and testing of new treatments. For example, transgenic mice expressing mutations in the specific gene known to cause a genetic disease in humans (e.g. Alzheimer's, Huntingdon's chorea, Friedrich's ataxia, cystic fibrosis etc) have provided enormously valuable, and previously unavailable animal models of the disease for analysis and testing of new treatments.
- For example, rodents do not exhibit Alzheimer's disease so no rodent model was available. There is now a genetically modified mouse model: mice which have been genetically modified to express the B-APP gene with the mutation known to cause AD in humans, exhibit the behaviour and pathological features of the disease. These mice have proven invaluable in a long series of experiments to develop and test antibodies to treat the disease, which are now in clinical trials. Several studies have been published recently.
- "Transgenic and knock-out mouse models have already been made which have explained the molecular basis of human diseases; development of new therapeutic strategies can then be based on these model systems. Transgenic mice have also been used ... to analyse complex biological systems such as the many facets of the immune response. One particularly useful transgenic organism is the 'humanised mouse' carrying the human SXR receptor, which enables the mouse to respond to foreign molecules in the same way as humans. Another example is the range of mouse models for studying human cancers, in which key genes such as p53 and mdm2 have been deleted: these animals become very sensitive to carcinogens and can be used to detect carcinogenic effects which might otherwise be missed. Another very useful and informative transgenic strain has been the 'Immortomouse', carrying the SV40 T antigen, from which cells of any body tissue can behave as immortal cancer cells. The amount of highly relevant and directly informative data coming from these animal experiments will continue to increase for some years to come" (Anon.).
- Transgenesis permits more precise animal models to be developed and may improve scientific insight, while often reducing the severity of procedures used in existing animal models. Examples of transgenic models include:

- Transgenic sheep: production of therapeutic protein products in the milk, to treat diseases such as certain types of blood clotting disorder
- New ways of studying arthritis, with pathological features of greater specificity and lesser severity than previously existing models.
- Numerous examples of enhanced understanding of the function of different genes (e.g. much improved understanding of the immune system and responses to infections).
- Carcinogenicity studies in transgenic rodents e.g. p53 hemizygous mice; these use fewer animals and are of reduced duration compared to traditional studies.
- Neurodegenerative disorders – there is potential for improved animal models which will reduce need for testing using less predictive procedures.
- Ocular disease – natural and transgenic mouse models have been integral in developing innovative gene therapeutic approaches (in academia) for the treatment of currently incurable inherited retinal degenerations leading to blindness.
- The use of transgenic animals as a source of tissues for transplants (xenotransplantation).
- "Humanisation" of rodent models may ultimately reduce the need to use higher mammalian species such as the dog or primates during drug development or testing.

ANNEX F

COST-BENEFIT SCHEME SUGGESTED BY THE ANIMAL HEALTH TRUST WITH AN EXAMPLE

Cost/ Benefit Analysis

Summarise costs and benefits associated with the programme of work

Costs	Benefits
Acquisition For influenza, naïve ponies are obtained from Wales. There will be stress associated with capture, transport and quarantine procedure. Transport of ponies to the challenge facility will entail some stress to the ponies. Some homebred ponies may be used. If ponies from different social groups (e.g. homebred and procured ponies) are mixed, this may involve some stress until a new social hierarchy is established.	**Improved prevention and/or treatment of equine influenza** Testing of pharmaceutical products is essential to ensure that high standards regarding efficacy and safety are met before new or updated products are issued for field use. Traditional inactivated equine influenza vaccines are currently available worldwide and may be responsible for sparing hundreds of horses from the effects of equine influenza each year. On rare occasions, equine influenza has been responsible for the deaths of hundreds of animals (e.g. in China in 1989 when an 80% mortality rate was recorded in an outbreak of equine influenza). In the event of outbreaks caused by novel strains such as that in China in 1989, alternatives to vaccines such as antivirals may help reduce the death toll.
Husbandry and Care Stress of being housed in an outstation or specified contained environment facility (for a limited period), i.e. boredom due to restriction to natural behaviour in this environment (e.g. no grazing).	**Reduction of experimental animal usage** Where possible, use of animals is reduced, for example as a result of accumulated evidence from previous studies that the SRH antibody response is an adequate surrogate marker for efficacy of inactivated equine influenza vaccines, it is now not necessary to perform challenge trials if an influenza vaccine is merely updated with regard to strain content, efficacy is assessed by serological response alone.
Procedure Discomfort due to vaccination and/or treatment and sampling procedures. Physiological stress if influenza clinical signs are produced, although the disease induced in experimental equine influenza challenge studies is usually moderate and self-limiting.	**Broader application of some vaccine delivery/adjuvant systems** As the experimental influenza challenge procedure employed at our establishment is well defined as a measure of vaccine efficacy, this may be used as a proof of concept for novel adjuvants/vaccine delivery systems that could be applicable to vaccines against other diseases of the horse and

	other species. In this case, it is more difficult to quantify the numbers of animals that could benefit as a result of trials conducted in a small number of ponies.
Fate Animals will be returned to pasture. They will then either be re-used in another project or discharged from control of the Act (re-homed/returned to supplier).	
Numbers The project licence permits the use of up to 210 equidae per year for trials involving viral agents including equine influenza. In addition, the use of up to 6000 eggs is permitted (the actual numbers of eggs used is dependent on the number of challenge studies conducted). There are practical restraints on how many trials involving equine influenza virus can be conducted in any year and it is unlikely that more than 2-3 large trials using 30-40 animals will be conducted in any one year throughout the 5-year period covered by this application. The number of ponies used each year can vary greatly, for example 109 ponies (4 studies) were used in 1999, 79 (2 studies) in 2000 and 21 (one study) in 2001.	
Explain why you judge that the benefits clearly outweigh the costs.	
The likely costs to animals used in this programme of work are regarded as being mild to moderate (due to procurement, containment, experimental procedures and infection). Around 20 to 100 animals will be used per year but not all of these will be subjected to challenge. It is anticipated that in challenge studies, groups receiving vaccination or treatment will be protected, to a varying degree, against the likely disease symptoms. Hence only the control groups are likely to experience the full adverse effects resulting from challenge. Measures as described (e.g. prophylactic administration of antibiotics) will be taken to ameliorate the potentially more severe adverse effects. The potential benefits to hundreds, if not thousands, of equidae worldwide (only New Zealand and Australia remain free from equine influenza) must be weighed against these costs. Inactivated equine influenza vaccines have been available since the 1960s. Studies such as those proposed in this programme have led to improvements in the level and duration of immunity induced by these vaccines through the use of better adjuvants with reduced side effects compared to the mineral oil adjuvant used in some early vaccines. However, influenza viruses are very plastic in their nature, undergoing a process known as antigenic drift, which enables the constantly evolving virus to evade neutralisation by antibodies induced by earlier strains. Previous challenge studies have demonstrated the need to regularly update the vaccine strains to keep pace with changes in the circulating field strains. If vaccines fail to keep pace with variation in the field, the result can be major vaccine breakdown as occurred during the 1989 epidemic,	

which affected horses throughout Europe and North America. Where effective vaccines are in place, it is difficult to place a figure on the numbers of animals that have benefited from protection against disease. Regular vaccination of competition animals is mandatory in the UK, and in the past few years there have only been sporadic outbreaks, with only one outbreak occurring in horses of mixed vaccination history in 2001. In contrast, in Sweden, where mandatory vaccination was abandoned as vaccines were perceived to be ineffective (due to them being outdated) there were around 40 outbreaks of equine influenza last year. The long history (>20 years) of equine influenza challenge studies in the host animal at our establishment means that this is a well established method and has enabled a good immune correlate for protection (antibody measured by the single radial haemolysis test) to be established for inactivated vaccines. This in turn has enabled legislation to be put in place that permits the updating of vaccine strains on the basis of serological data only, i.e. without the need to subject animals to challenge studies. Challenge studies nonetheless continue to be important for the development of improved vaccines and for the assessment of potential antiviral agents, and the challenge model established for equine influenza is highly suited to testing novel adjuvants, vaccine delivery methods and drugs that may be also applicable to other diseases and benefit not only horses but other species as well.

As with human influenza, equine influenza is often underrated as a disease because symptoms are generally moderate and the disease is usually self-limiting. However, it is one of the major causes of respiratory disease in horses worldwide. Mortality is rare but the disease tends to be more severe in donkeys (there was high morbidity and mortality amongst donkeys during an outbreak in India in 1987) and foals and in pregnant mares prolonged pyrexia may result in abortion. Although only 2 subtypes (H7N7 and H3N8) of influenza are known to affect horses, there are many other subtypes present in the avian populations of the world and emergence of a new subtype into the horse population could occur. The potentially devastating effect this could have was demonstrated in China in 1989 when an H3N8 virus was transmitted directly from birds to horses (i.e. re-emerged). Although this virus did not spread outside of China and did not become established in the horse population, it caused a widespread epidemic with an 80% mortality rate. Current inactivated vaccines would not be effective against a newly emerging strain of influenza, hence the interest in the development of antiviral agents and other drugs. Vaccines that stimulate a broader immune response including cellular immunity (e.g. live attenuated vaccines, vector delivery vaccines) may also offer greater protection against newly emerging strains.

There is little doubt that studies such as those proposed in this programme, involving relatively few animals and carried out under controlled conditions, have benefited a great number of animals already, but equine influenza continues to be a threat. Due to the variable nature of the virus, it is unlikely that it can be eradicated but it may be possible to improve control of the disease and to be better equipped to respond to newly emerging strains through the development of novel vaccines and drugs.

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