A COMPARISON OF THREE MODELS FOR ETHICAL EVALUATION OF PROPOSED ANIMAL EXPERIMENTS[1]

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Abstract *Animal Welfare 1994, 3:* 107-128

Three recently developed and published schemes to evaluate the acceptability of proposed animal experiments are discussed and compared:

1. *The model developed at the request of the Dutch Veterinary Public Health Chief Inspectorate by the Department of Animal Problems of Leiden University (the 'Dutch Model');*
2. *The model proposed by the Canadian, David G Porter (the 'Porter model');*
3. *The model developed by the British Institute of Medical Ethics, published in* 'Lives in the Balance: The Ethics of Using Animals in Biomedical Research' *(the 'IME model').*

It is concluded that the Porter model, although compact, does not have an acceptable level of discrimination; nor does it provide the researcher with any pragmatic tools to optimize the research design. The other models appear to be quite adequate for the different purposes for which they were developed. The Dutch model was developed to guide the evaluation procedure at the level of local institution-based committees (ie internal evaluation by colleagues), whereas the IME model will serve the professional officers of the United Kingdom Home Office Inspectorate (ie external evaluation).

Finally, the pragmatic consequences of the three models are discussed with respect to two hypothetical cases.

Keywords: *animal experimentation, animal welfare, cost benefit analyses, ethical decision models*

Introduction

Various models have recently been developed to offer animal research ethical review committees guides for their task. In this paper we will focus on the following three models:

1. The model developed by the Department of Animal Problems of Leiden University (Theune & de Cock Buning 1991). The development took place at the request of the Dutch Veterinary Public Health Chief Inspectorate which is responsible for the implementation of Dutch law on animal experimentation. This model will be called the 'Dutch model' in this paper (see Appendix).
2. The model developed by the British Institute of Medical Ethics which was published in '*Lives in the Balance: The Ethics of Using Animals in Biomedical Research*' (Smith & Boyd 1991). This model will be referred to as the 'IME model'.
3. The model proposed by the Canadian, David G Porter (1992) which will be referred to as the 'Porter model'.

It is important to realize that these models were developed in the context of the cultures existing in the countries of origin. They aim to meet specific problems which feature in the process of ethical reflection in each particular country in the early nineteen-nineties. Every country has followed its own unique track in this process from different historical starting positions. Therefore any comparison of these models must take into account the international differences in licensing systems; the systems of review committees, and the socio-cultural climates regarding animal experiments. We will first sketch the context in which the Dutch model operates followed by a brief description of the model. The differences will be analysed with respect to the IME and the Porter models. Finally, these differences will be placed in a wider context addressing the general principles underlying the models.

The Dutch model

In the Netherlands every research institute (university or industry) performing animal experiments possesses at least one Local Science Committee (LSC) to evaluate the scientific merits of research proposals at the level of the faculty of universities and of the scientific board in industry. About ten years ago most institutes established institutionally-bound review committees to evaluate the acceptability of animal experiments (Animal Experimentation Committees; AEC). Every research proposal detailing intended use of animals has to obtain the approval of the LSC and the AEC. In addition, by law, an Animal Welfare Officer is contracted by the institute to advise researchers about improvements for animal welfare. Research institutes are unexpectedly visited by regional Veterinary Inspectors of the Veterinary Public Health Chief Inspectorate. The Inspectorate might withdraw the institution's licence to perform animal experiments if the regulations are not followed. One of the prescriptions is the European Economic Community (EEC) prescription that those involved in animal experimentation have to be competent. The Animal Welfare Officer verifies within the institute whether the researchers and biotechnicians meet the requirements ordained by the law.

A form was developed in the Netherlands for completion by all research institutes wishing to submit projects to their AEC. Through this form the researcher's attention is immediately drawn to a number of ethically relevant aspects:
- qualifications of the people involved;
- endorsement by LSC (or even better, support from a major public funding agency);
- justification for the species and number of animals;
- likely severity of the adverse effects caused by housing and experimentation;

- justification of the analgesia;
- justification of not using replacement alternatives;
- justification of the aims;
- significance of the project.

The estimation of pain and distress experienced by the animal is scored at three levels (minor, moderate and severe) in combination with four durations (under one day; 1 to 7 days; 8 to 30 days, and over 30 days). According to recent advice from a special working group of the National Committee on Animal Experimentation – an independent committee which advises the Minister of Public Health – the three levels of pain and distress should be based on physiological and behavioural signs rather than on a (black)list of scientific procedures. The philosophy underlying this advice is, among other considerations, that skilful investigators might be able to perform experiments which are labelled as severe without inflicting more than moderate distress on the animals. It would be incorrect to treat these investigators as if they were no better than a moderate investigator (and vice versa), who would probably inflict severe harm on the animals. It is important to mention that this model stimulates continuous feedback from the animal caretakers towards the investigator and the committee.

Another feature of the Dutch system is the direct communication of the local Animal Welfare Officer with all people who handle the animals. The Officer's approval is often compulsory before a project can be evaluated by the committee. This means that most Laboratory Animal Science (LAS) aspects (health, housing, management, alternatives) are checked before the committee even starts a review. The committee thus enjoys the luxury of judging projects which are relatively sound with respect to the scientific methodology and LAS aspects. They 'only' need to balance the scientific significance of the project against the cost to the animals. Because a generally accepted model to estimate the amount of distress caused by scientific procedures is already available, what remains is the problem of assessing the significance of the experiments. Therefore, in the Dutch model emphasis is laid upon the assessment of the relevance of the human (or animal) interest involved.

The Dutch designed a rather detailed checklist to ensure that all relevant moral aspects would be on the agenda of the committee, so that they could make a clear 'Yes' or 'No' decision. This checklist, which did not exist before, pairs a large number of subtle moral aspects to a high degree of discrimination.

The questionnaire was optimized by studying numerous cases and by consulting representatives of some of the major research institutes and Inspectors of the Veterinary Public Health Chief Inspectorate. Their Department of Animal Experimentation is the governmental department in charge of monitoring the law on laboratory animals in the Netherlands.

The checklist helps the making of clear decisions. It will broaden and deepen the discussion in animal experimentation committees. Moreover, a properly completed checklist-form might very well serve as a 'document of argumentation' for anyone who wants to question an animal care committee's decision. The checklist might also serve as a discussion paper in the public debate on animal experiments: on the basis of it one can argue for and against proposed aspects. (The philosophical presuppositions are discussed in Theune & de Cock Buning 1992.)

The Dutch model consists of four parts in which a) 'quality of the animal experiment', b) 'discomfort', c) 'significance' and d) 'credentials of the research group' are assessed. Each part contains detailed questions to help the committee members trace morally significant aspects of a proposal. The questionnaire is designed in such a way that by circling the chosen answers one obtains a visual impression of the overall score: positive (right side), or negative (left side; see Appendix). In order to avoid visual overestimation, the design is such that all questions are necessary and are independent of each other. In this way each part will lead to a qualitative conclusion (minor/moderate/great; sufficient/insufficient). The four conclusions are used in the next phase as the input for a decision tree, resulting in a straightforward judgement.

Because the construction of this decision tree is crucial for the outcome, some of the main underlying considerations will be discussed briefly. First of all, the sequence of the four aspects within the decision tree is not without relevance. When the evaluation of the first part (a) immediately leads to rejection, even brilliance of the other three parts (b-d) can obviously not compensate for the weakness of the first. In other words, the earlier an aspect is evaluated in the decision tree the more it can work as a limiting factor. In the Netherlands it is generally accepted that *only* a sound research design can justify animal experiments. Therefore, we make the assessment of the scientific and LAS aspects the first step. This is also common practice in the Netherlands with other review agencies, ie the LSC and the Animal Welfare Officer approve the application before it is evaluated by the AEC.

The structure of the decision tree with respect to the other three parts becomes fixed when it is realized that the 'credentials of the research group' (a positive attitude towards the 3Rs), ie part d, is less important than the decision of weighing 'discomfort' against 'significance'. Consequently, the tree takes the appearance of Figure 1.

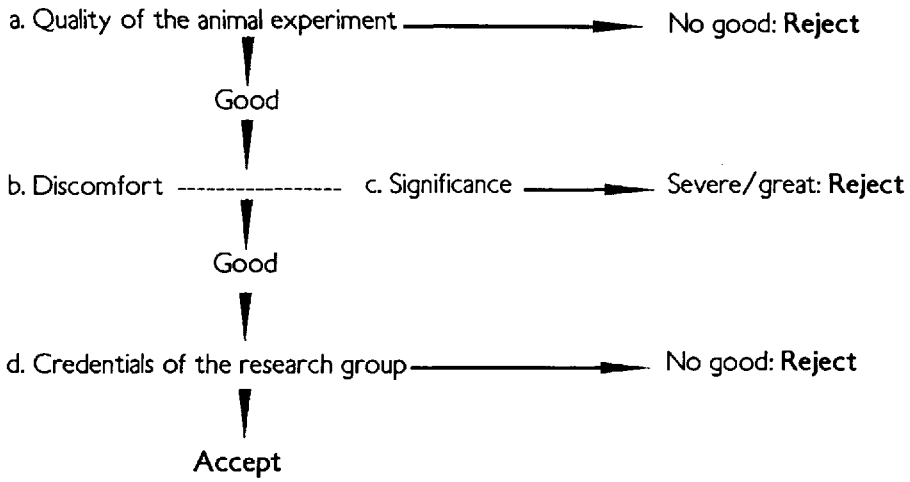

Figure 1 **Decision tree used in the Dutch model in deciding whether to accept or reject an animal experiment proposal.**

Balancing three levels of discomfort (minor, moderate, severe) against three levels of significance (minor, moderate, great) results in nine combinations (Table 1).

Table 1 **Designation of approval and rejection at nine combinations of discomfort and significance.**

	Discomfort		
Significance	**Minor**	**Moderate**	**Severe**
Minor	Reject	Reject	Reject
Moderate	Approve	Approve	Reject
Great	Approve	Approve	Approve

The designation of approval and rejection on the discomfort/significance balance is decided upon after due consultation with the National Inspectors of the Animal Experimentation Department of the Veterinary Public Health Chief Inspectorate. This weighing matrix is slightly more restrictive than most researchers are inclined to formulate. Researchers usually prefer to approve a combination of minor discomfort and minor significance. Pressure groups in our society, however, even prefer a ban on experiments of moderate significance and a moderate level of discomfort. We think that this attribution realistically describes the current tension in the ethical debate in the Netherlands.

As stated above, the emphasis of the Dutch model lies upon the assessment of the relevance of the human (or animal) interest involved in the project. Five areas of interest are distinguished, each demanding a specific approach to assess its merits (see Appendix):

- *routine research (Cr)*
- *diagnostics (Cd)*
- *education (Ce)*
- *problem oriented research (Cp)*
- *basic (fundamental) scientific research (Cf)*

The Dutch law on animal experiments mentions two interests that may justify animal experiments: they must either be of interest to the health or nutrition of man or animal or they must be of scientific interest. All other interests need explicit approval by the Minister of Public Health. So, the crucial question regarding the first four areas of interest is to what extent the results of the experiments will contribute to better health or nutrition of man or animal.

Regarding the assessment of the interest of routine research (*Cr*; testing, production and control), a distinction between the 'importance of the actual animal-experiment under concern' and the 'significance of a (possible) product' appears to be most fruitful. The former formulation refers to the production, efficacy and safety of a substance. The significance of the substance is a separate issue (eg the importance of testing the safety of a 'new' cleaning product against the significance of the cleaning product itself).

Assessment of interest with respect to animal experiments in the context of diagnostics (*Cd*) and education (*Ce*) appears to meet little difficulties. Assessment of the interest of problem oriented research (*Cp*; for the health and nutrition of man or animal) resembles the ethical debate in the field of medical health policy which focuses on the necessity to make a choice as a consequence of the scarcity of money. It is an illuminating exercise to ask oneself the question 'Which projects would survive if one knew that only 30 per cent of the applications were supported?' Every project may be interesting enough to support when considered on its own. However, when one is forced to choose, liberal ethicists (favouring individual freedom and personal responsibility) are interested in whether the illness of the patient is due to him/herself or not, whereas utilitarian ethicists are interested in the overall number of people (animals) who (which) will benefit from the results as well as the magnitude of the problem. Because both questions have their merits in different cases, both are introduced (*Cp 1.1, 1.2, 1.3*; Appendix).

Problem oriented research using animals for human problems presupposes a reasonable extrapolatability. This depends on to what extent the disease develops in the same way in animals as in humans and to what extent the animal functions in a way similar to humans, in terms of anatomy, metabolism and behaviour (*Cp 1.7* and *2.4*).

Assessing the specific interest of basic (fundamental) scientific research (*Cf*) amounts to whether the project contributes substantially to the body of scientific knowledge. The questions listed here are the same as those asked by general funding agencies for basic research (position within the relevant scientific network, validity of the method, scientific challenge).

Comparison with the Porter model

The Porter model consists of only eight questions. Six of these questions are directly addressed in the Dutch and IME models. The questions *C* and *F* appear to be unique to the Porter scheme; see Table 2.

Table 2 Comparison of the Porter model with the Dutch and IME models.

Porter model	Dutch model	IME model
A Aim of the experiment	Yes	Yes
B Realistic potential to achieve objective	Yes	Yes
C Species of animal	(Indirect)	(Indirect)
D Pain likely to be involved	Yes	Yes
E Duration of discomfort or stress	Yes	Yes
F Duration of experiment as proportion of lifespan	No	No
G Number of animals	(Indirect)	Yes
H Quality of animal care	Yes	Yes

The explicit emphasis on the animal species (question *C*) seems to be absent in the other two models, but is actually incorporated in the level of discomfort in the other models. In the Dutch and IME models this level is assessed by means of species specific physiological and behavioural parameters. This approach was initiated by the pioneering work of Morton and Griffiths (1985) to assess pain and distress in animals. However, the Porter model also refers to Morton and Griffiths in relation to question *D*. This results in a duplication of the species aspect in two different questions which were supposed to be independent. In other words, the species aspect is weighed twice in the Porter model.

The second question unique in the Porter model is *F*: it links the duration of the experiment with the lifespan (LS) of the animal species involved. An eight hour experiment with mice (lifespan one year) will score 10^{-3} LS and will be considered 'moderate' (3 points). The same experiment with chimpanzees (lifespan fifty years) will score $2x10^{-5}$ LS, which will be regarded 'extremely short' (1 point). This approach may stimulate researchers to use animals with a long lifespan in order to decrease their overall score. There might be some rationale for the lifespan idea: small animals with a high metabolism rate usually live shorter lives and it is often suggested that they live more 'intensively'. However, one must realize that chimpanzees, for example, are also considered to be the more sentient (or more conscious) animals, in contrast to mice or frogs. This idea, however, interacts negatively with the species score of question *C*! In other words, question *F* may stimulate research with more conscious animals which is not in concordance with the principle of replacement (Russell & Burch 1959) and is not independent from questions *C* and *D*.

The claim for independence is crucial for the Porter model, because it is designed as a 'credit-point' system. The eight questions will evaluate a project in the form of a score between 8 and 40. Porter proposes that acceptable projects should score under 22 (maximum 7 for *A-B*, maximum 15 for *C-H*). But at the same time Porter seems to undermine the credit-point philosophy behind his model by remarking that 'perhaps a unit of ethical concern is needed where a mollusc might score one and a chimpanzee 1,000,000.'

There are also some aspects missing in the Porter model which are included in the other two models. For instance, these eight questions do not encourage the researcher to justify why *in vitro* methods are not possible. In contrast to the explanation in the text, namely the explicit Schweitzer perspective (ie to avoid harming sentient animals whenever possible), the model does not award thorough justification by the researcher. A possible question formulated in the approach of the Porter model might be: 'Convincing reasons for using animals: Yes = 1, Doubt = 3, No = 5'. This point also illustrates another consequence of the Porter approach. Even when the rationale is inadequate, the project might still be approved when the other scores do not exceed 22 (or 23 with the additional question). This situation cannot occur in the Dutch model because of the construction of the decision tree and it is at least signalled in the IME model (question *2.2.2*: 'Necessity to use animals in the procedures').

Comparison with the IME model

In the United Kingdom (UK) every researcher or biotechnician has to acquire his/her own personal licence which describes in detail the competence of that person. Additional courses might extend the personal list of skills and licences. In addition all plans for animal

experiments have to be submitted for a project licence. An independent and centrally based body of Inspectors of the Secretary of State at the Home Office keeps watch over the licensing system and regularly visits all research groups. Approval of a project is given by the Home Office Inspector. The British IME model was developed in the context of an extensive project and personal licensing system, which is reviewed by a well-trained Inspectorate to advise the Home Secretary (Table 3).

Table 3 **Items of the IME model compared with the Dutch model (numbers of questions dealing with the item) and Porter model; (...) indicates implicit or partly.**

	IME model	Dutch model	Porter model
***1* Assessment of the potential benefits of the project**			
1.1	Value – social	11	*A*
1.2	– scientific	1	*A*
1.3	– economic		
1.4	– educational	2	
1.5	– other	5	
1.6	Originality	(1)	
1.7	Timeliness	1	
1.8	Persuasiveness	2	
1.9	Applicability	6	
***2* Assessment of the proposed approach**			
2.1.1	Relevance of approach to potential benefits	4	
2.1.2	Quality of hypothesis	2	
2.1.3	Quality of experimental design	1	
2.1.4	Background research	3	
2.2.1	Applicability of scientific procedures	1	
2.2.2 i	Necessity of animals	1	
ii	Necessity of species	(1)	
2.2.3 i	Necessity of procedure in relation to severity		
ii	– in relation to number	1	
2.2.4	Maximization of information	1	
2.3.1 i	Training of staff	(1)	
ii	Experience of staff	3	
iii	Competence of staff		
2.3.2	Quality of equipment and facilities		
2.3.3	Adequacy of funding		

Continued

Table 3 *Continued*

***3* Overall assessment of the project: assessment of *likely* benefits**				
3.1		Overall potential benefits	5	
3.2	*i*	Likelihood of realization	2	*B*
	ii	– in time		
3.3		Necessity of approach (3Rs)	1	
***A* Quality of facilities and project workers**				
A1.1		Quality – housing		*H*
A1.2		– equipment		*H*
A2.1		– assisting staff		*H*
A2.2		– performing staff		
A2.3		– responsible staff		
B* Severity of effects of husbandry and procedures on animals set in the context of the assessment in part *A				
B3.1		Severity of distress for the species		
B3.2.1		– during capture and transport		
B3.2.2		Threat to wild population		
B3.2.3		Adaption to laboratory		*E*
B3.3		Genetic defect	3	
B4.1		Housing	3	*E*
B5.1		Scientific procedures	(2)	*(D,E)*
B6.1		After analgesia	2	*D,E*
B7.1		Number of animals	(1)	*G*
C		**Overall costs**	I	

(after Smith & Boyd 1991)

A comparison of the IME model and the Dutch model reveals a strong emphasis on technical aspects of laboratory animal science in the IME model, as exemplified in *2.3.1-2.3.3* and *A1.1-A2.3*, which appears absent in the Dutch model. As stated above, however, one should realize that in the Netherlands these aspects are evaluated by the Animal Welfare Officer at an earlier stage. An aspect which is indeed lacking in all the phases of the Dutch evaluation procedures is the cost of using animals taken from the wild (*B3.2.1-B3.2.3*). This is a valid point which certainly deserves to be incorporated.

The large number of questions in the Dutch scheme regarding 'social value' (*1.1*), 'applicability' (*1.9*) and 'overall potential benefits' (*3.1*) shows how this model covers these aspects in five series of detailed questions on the significance and value of five main fields in animal research (see Appendix). Apart from splitting up the question for significance, the Dutch model formulates several aspects which are not addressed in the British model. They are listed below together with the ideas behind these questions (Table 4).

Table 4 **Motivation for more detailed questioning in the Dutch model compared to the IME model.**

	Question	Motivation
A1.2	Approval of the research design by a statistician?	Bad research design can never justify animal experiments.
A1.3	Existence of pilot studies?	A necessity to estimate the number of animals by means of a 'likelihood' approach.
A1.4	Will the animals be used again with severe discomfort?	Minimizing discomfort.
A3.2	Is it a case of repeated research?	Principle of reduction.
A3.3	Does closely related research occur elsewhere?	Principle of reduction.
A3.4	Are organs/animals shared with others?	Principle of reduction/efficiency.
A4.4	Is the discomfort per animal reduced by increasing the number of animals?	Primacy of reduction of suffering over reduction of numbers.
Cr1.1	Is the animal experiment compulsory by law?	Tracing the responsibility.
Cp1.4	What is the extent of the health benefit expected from the new or improved therapy/product/method?	Assessment must be based on facts instead of hope.
Cp1.5	What is the extent of the contribution to improvement of therapy/product/ method from this concrete experiment?	Actual relation between short-term and long-term goals.
Cp1.7	Is the animal model extrapolatable?	Be efficient.
Cf1.3	What is the scientific content of the research project?	Be efficient.
D1.2	Does the group often conduct pilot studies only?	Be efficient.
D1.5	Does the group develop alternatives on its own or does the group participate in validity research?	Stimulating a climate for the 3Rs.
D1.6	Do the researchers get/create sufficient opportunities to look for alternatives?	Stimulating a climate for the 3Rs.

Thus we hope to help uplift and improve stagnating discussions in Animal Experimentation Committees (AEC) and to provoke stronger arguments than before. The following three examples illustrate some other consequences of the Dutch model.

Example number one: at an agricultural university much research is carried out in order to improve the conversion of nutrients in cattle intended for meat production. Researchers

tend to justify this research with the argument that they aim to improve meat production and subsequently the world food situation. According to the checklist they now have to answer the following question: How large is the expected contribution to the improvement of the health or nutrition of humans or animals (*Cp 1.4* and *1.5*)? This contribution will not always be very large, because such high-efficiency stock cannot be bred in developing countries; cattle in Western countries consume food that is imported from developing countries and as far as an improvement of nutrition level in Western countries is required there may be other ways than improving the conversion efficiency of cattle. This means that the decision of a committee may have consequences at a social and political level.

A second example is concerned with interests in the short and long term. The checklist discriminates between research projects that have health or nutrition as a main interest and projects that have these as a secondary interest. For instance, the main purpose of cosmetic research is to develop new competitive products. Of course, these products must be tested for safety, efficacy and quality, before they can be released on the market (*Cp 1.1*: short-term interest related to toxicity testing). But given the fact that testing will involve laboratory animals, the committee should assess the long-term interest of the products to humans or animals (*Cp 1.4*). The crucial question should therefore be: Are these products in the interest of the health or nutrition of man or animal? This may produce some interesting discussions in the local (industrial?) committees.

A final example is concerned with scientific research performed at universities, for instance basic medical or veterinary research. Such research often has a double interest: it is both in the interest of the health of man or animal and of scientific interest. Discussions in AECs shift from one interest to the other. A lack of 'good reasons' for the scientific interest tends to be compensated for by a marginal health aspect. As a consequence, decisions become very unclear and the justification of research projects that score low on both interests may be questioned. We recommend that committees should first identify the main interest and assess only this, leaving the other one out of the discussion. Otherwise, a vague research project may in the end be given permission which cannot be clearly justified. In the case of scientific interest, a call on academic freedom will not be satisfactory because the well-being of animals is at stake. The scientific merit of the project must be assessed according to the usual quality criteria used by scientific review boards.

Discussion

An interesting question is to what extent these three different models give rise to differences in final judgment. Instead of designing several test cases, we chose the four test cases used by Rebecca Dresser (Dresser 1989) to analyse the decisions of 32 committees. Two cases only are discussed here in detail.

Case 1: production of monoclonal antibodies

In the context of basic research for vascular diseases, monoclonal antibodies (MAB) against vascular smooth muscle proteins are produced in 200 mice by means of two successive steps, as follows: first the antibody response against this protein is enhanced by an initial footpad injection of Freund complete adjuvant and subsequent injections with Freund incomplete

adjuvant. Test samples are collected from the orbital sinus of non-anaesthetized mice. Subsequently, immune reactive cells from the spleen are fused with tumour cells to create hybridoma cells. These cells are injected into the peritoneal cavity of other mice to produce ascites fluid containing the MAB. For four weeks the researcher collects the ascites fluid weekly. No anaesthesia is used, and all mice are killed humanely by means of cervical dislocation. The outcome of assessment is as follows:

Dresser
Contingent approval (13 committees), deferral (18 committees), disapproval (1 committee). Arguments: no footpad injection of Freund complete adjuvant allowed; no orbital blood collection without anaesthesia allowed; daily monitoring of mice with ascites tumours necessary; no justification for number of mice (200); no justification of not using alternatives; inadequate description of actual goal; qualification of staff unknown.

Porter model
31-33 points, which means rejection. This score can only be improved by a better objective than fundamental research (*A*:5) and a lower number of animals to be used (*G*:5). Even these modifications would not be sufficient to reach the limit of 21.

IME model
Part *1* (potential benefits): scores low to medium
Part *2.1* (scientific merit): scores low to medium
Part *2.2* (scientific procedures): scores low
Part *2.3* (quality of staff and facilities): scores medium to high
Part *A* (facilities and staff): scores medium
Part *B* (severity): scores medium to high

Dutch model
If the LAS aspects are improved (anaesthesia: [part *A*] rejection), moderate discomfort balanced against moderate significance will result in approval, if the skills and conscientious attitudes of the researchers are positive.

Case 3: neurophysiology data of neuronal learning processes in the brains of cats
Three electrodes are placed in each of 14 mixed breed cats under anaesthesia. Postoperative antimicrobial drugs are administered. Three days later, cats are given a neuromuscular blocking agent, intubated with a catheter coated with a local anaesthetic, and placed in a stereotaxis apparatus with an atraumatic head holder. A micro-electrode is placed in the brain, and the three other electrodes are randomly stimulated. Activation of the neuronal cells is recorded for up to two hours, after which the cats are humanely killed with sodium pentobarbital. The outcome of assessment is as follows:

Dresser
Approval (1), contingent approval (2), deferral (18), disapproval (11).
Arguments: muscle paralyses without proper anaesthesia criticized; this could only be approved if the cats' conditions were closely monitored (heart rate, blood pressure, pupillary response) to avoid pain and distress; justification needed of the stereotactic apparatus; justification needed of the scientific merit; justification needed of the number and species of animals.

Porter model
22-25 points: results in rejection. If proper anaesthesia is given 22, otherwise 25 points. Reduction of the score (by 2 points) by means of a lower species is possible, if the learning hypothesis can be tested in fish and frogs.

IME model
Part *1* (potential benefits): scores low to medium
Part *2.1* (scientific merit): scores low to medium
Part *2.2* (scientific procedures): scores low to medium (applicability: high)
Part *2.3* (quality of staff and facilities): scores medium to high
Part *A* (facilities and staff): scores medium
Part *B* (severity): scores high (after proper anaesthesia low to medium)

Dutch model
Quality of the animal experiment (part *A*) could be improved (experiment now rejected). After improvement (anaesthesia) 'moderate' discomfort is balanced against 'moderate' significance of the project which will result in approval, if the credibility of the group is judged sufficient. Deciding aspects: *Cf 1.2* (scientific quality), *Cf 1.4* (chance of success).

Table 5 Comparing the scores of the three models with the four cases of Dresser.

Dresser[1]	Porter[2]	IME[3]	Dutch
Case 1: Approval	31-33: Rejected	Medium	Approval
Case 2: Deferral	28: Rejected	Low-medium	Rejection
Case 3: Deferral	22-25: Rejected	Low-medium	Approval
Case 4: Disapproval	26-30: Rejected	Low-medium	Rejection

[1] Conclusion reached by most of the 32 committees.
[2] A score higher than 21 indicates a rejection of the project.
[3] Overall estimation of the justification of the project (low/medium/high).

The comparison above, and in Table 5, shows that with respect to these rather fundamental research projects the Porter model scores almost inversely to the 'common sense' practice of the committees analysed by Dresser, ie the least problematic case (Case 1) gives rise to the highest score, and the cat case (Case 3) might be acceptable when performed on lower animals.

Second, one learns that the Porter model is of little help to the researchers to improve the design of the project, since all projects will be rejected for their characteristic aspects.

Both the IME and Dutch models address the aspects signalled by the 32 Dresser committees. One difference is the lack of an algorithm in the IME model to reach a decision in a consistent way. The other difference is demonstrated by Case 3 where the Dutch model approves the project in contrast to the 'deferral' judgement of Dresser's committees and the low-medium judgement of the IME model. Pivotal to the Dutch decision is the structure of

the decision tree, which prescribes that 'moderate' discomfort is in balance with 'moderate' (scientific) interest (when the research group did not lose their credits). As remarked earlier, some groups in Western society might consider this as too 'pro-science'. On the other hand, the 'deferral' and 'low-medium' conclusions will most probably lead to a visit from the Animal Welfare Officer (or Home Office Inspector) to discuss the possibilities of optimizing the LAS aspects and to judge the humane attitude of the researchers. If the LAS aspects (part *A* of the Dutch model) can be improved satisfactorily, and if the skills and attitudes of the researchers appear to be adequate (part *D* of the Dutch model), the IME model and Dresser's committees will probably ultimately result in the same decision as the Dutch model.

Which model will serve best depends mainly on the context in which it has to function. This implies that one has to reflect on the purpose of such models within the scientific community, namely a standard for the researchers to anticipate on (Porter model) or an educational tool to introduce ethical procedures and decisions to researchers and committee members. This aspect is clearly one of the goals of the IME and Dutch models. It is not enough for researchers just to write the concepts of 'reduction', 'refinement' and 'replacement' in gold. They, and members of animal experimentation committees, in fact ask for more concrete guidelines themselves. This is in concordance with the empirical rule from pedagogy 'the more insecure students are (and therefore hesitate to participate), the more rules the teacher must provide'. On the other hand, researchers are only human and they easily become irritated by detailed questionnaires and too many 'rules'. Both the IME and the Dutch models try to find a balance between these conflicting forces. The Dutch model elaborates, however, with regard to the assessment of interests, precisely because of the general hesitation of scientists to assess critically the significance of colleagues (all committees are institutional in the Netherlands).

One reason why the IME model does not elaborate on the interests might be the professional character of the Home Secretary's Inspectorate, which contrasts to the local committees in the Netherlands.

Although the IME and Dutch models are much alike as ethical models driven by some general principles (3Rs, efficiency principle etc), there is a notable difference with regard to the areas of possible interest. The IME model distinguishes 'social value'; 'scientific value'; 'economic value'; 'educational value', and 'other value', whereas the Dutch model does not accept an economic value as a relevant counterweight for animal discomfort. Besides the fact that this is a political choice it also clarifies our idea with respect to the responsibilities within an institution. It is argued that the committees have to refrain from management aspects which are the responsibility of another board. For instance, it would be unsound if the committee which has to judge the ethical acceptability of a research project, anticipates a possible overruling argument from the management board based on economic grounds. In the process of approval it must be clear – for everyone who wants to carry out an inquiry regarding a specific decision – what the ethical advice is and what the (overruling) decision of the management is. If the management board ignores internal advice, it is their responsibility.

For those researchers gifted with a humane attitude towards animals, the review models discussed above are probably superfluous. For many scientific workers, the 3Rs of Russell and Burch (1959) have proven to be real eye-openers. However, the models described above may be indispensable in changing the attitudes of researchers who are not always as humane as they should be.

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Appendix: checklist for the Dutch model

		Circle the answer of your choice	
A	QUALITY OF ANIMAL EXPERIMENTS		
1	**General**		
1.1	Has the scientific quality already been judged elsewhere as being 'good'?	No	Yes
	If not, did a statistician approve the research proposal?	No	Yes
1.2	Has a statistical account been given?	No	Yes
1.3	Is it a pilot study?	No	Yes
	If not, has a pilot study been done?	No	Yes
1.4	Are animals used again after an experiment which causes severe discomfort?	Yes	No
2	**Replacement**		
2.1	Have adequate sources (journals, databases) been consulted for alternatives?	No	Yes
2.2	Do alternatives exist?	Yes	No
	If so, what is your opinion about the reason for not using them?	Insufficient	Sufficient
3	**Reduction** of the number of animals		
3.1	Is it possible to perform the animal experiment with a smaller number of animals?	Yes	No
3.2	Is it a case of repeating research?	Yes	No
	If so, what is your opinion about the arguments in favour of repetition?	Insufficient	Sufficient
3.3	Does closely related research occur elsewhere?	Yes	No
	If so, does collaboration exist?	No	Yes
3.4	Are organs/animals shared with others?	No	Yes
4	**Refinement** (in consultation with animal welfare officer)		
4.1	Are pain and discomfort avoided as much as possible?	No	Yes
4.2	How is the prevention of pain and other discomforts?	Insufficient	Sufficient
4.3	Are the animals killed at a well-considered time and in a well-considered way?	No	Yes
4.4	Is the discomfort per animal reduced by increasing the number of animals?	No	N/A/Yes
4.5	Does the accommodation provide sufficient 'relief' for animals who emerge, ill or in pain, from an experiment?	No	Yes
5	**Judgement**		
	Quality of animal experiment?	Could be improved	Good
	Arguments in favour of dismissal		

B	DISCOMFORT FOR THE ANIMAL				
1	**Discomfort caused by experiments**				
	Experimental group 1				
1.1	What is the extent of the discomfort during the experiment?	Severe	Moderate	Minor	N/A
1.2	What is the duration of the discomfort in days?	>30	8-30	1-7	<1
	Experimental group 2 (control group)				
1.3	What is the extent of the discomfort during the experiment?	Severe	Moderate	Minor	N/A
1.4	What is the duration of the discomfort in days?	>30	8-30	1-7	<1
	Experimental group 3 (if applicable)				
1.5	What is the extent of the discomfort during the experiment?	Severe	Moderate	Minor	N/A
1.6	What is the duration of the discomfort in days?	>30	8-30	1-7	<1
	Experimental group 4 (if applicable)				
1.7	What is the extent of the discomfort during the experiment?	Severe	Moderate	Minor	N/A
1.8	What is the duration of the discomfort in days?	>30	8-30	1-7	<1
2	**Discomfort caused by housing conditions**				
2.1	Does the accommodation guarantee good physical health at the outset of the experiment?	No	Moderate		Yes
2.2	Does the accommodation impede species specific behaviour?	Severe	Moderate		No
2.3	Does the animal display abnormal behaviour caused by the accommodation?	Yes			No
3	**Judgement**				
	Discomfort for the experimental animal	Severe	Moderate		Minor
C	SIGNIFICANCE OF THE ANIMAL EXPERIMENT	**Please answer one cluster of questions only**			
Cr	ROUTINE RESEARCH				
	- production, control or biological standardization of sera, vaccines, diagnostica or other biological products				
	- production, control, or biological standardization of medicines				
	- production, or control of other medical or veterinary expedients or applications				
	- other biological standardizations				
	- testing of alternatives for animal experiments				
	- toxicity (routine) testing				
1	**Necessity of animal experiment**				
1.1	Is the animal experiment a liability?	No	N/A		Yes
1.2	If not, what is the extent of the (safety) interest regarding health and nutrition of man or animal?	Minor	Moderate		Great
2	**Assessment of the necessity of the product**				
2.1	How important is the product with regard to the health or nutrition of man or animal?	Minor	Moderate		Great
3	**Judgement**				
	Significance of the animal experiment	Minor	Moderate		Great

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Cd	**DIAGNOSTICS (identification and detection of diseases or other physical symptoms)**			
1	**Necessity of animal experiment**			
1.1	How important is the identification or detection for the health of man?	Minor	Moderate	Great
1.2	How important is the identification or detection for the health of animals?	Minor	Moderate	Great
2	***Judgement***			
	Significance of animal experiment	Minor	Moderate	Great
Ce	**EDUCATION (transfer of knowledge and proficiency training)**			
1	**Necessity of animal experiment**			
1.1	What is the importance with regard to the future health of man or animal?	Minor	Moderate	Great
1.2	What is the importance with regard to future handling of animals?	Minor	Moderate	Great
2	**Judgement**			
	Significance of animal experiment	Minor	Moderate	Great
Cp	PROBLEM ORIENTED RESEARCH **- research into course of a disease, pathophysiology, prevention, nutrition and housing** **- development of biological, pharmaceutical and biopharmaceutical products** **- development of toxicological and pharmacological methods** **- development of alternatives for animal experiments** **- development of transgene animals** **Either answer questions listed under 1 *or* 2**			
1	**Medical or veterinary significance**			
1.1	How severe is the disease?	Minor	Moderate	Great
1.2	How often does the disease occur?	Seldom	To some extent	Often
1.3	Can a high-risk group be indicated?	Yes		No
	If so, is it a large group?	No	To some extent	Yes
	If so, is the risk avoidable?	Yes	To some extent	No
1.4	What is the extent of the health benefit expected from the new or improved therapy/product/method?	Minor	Moderate	Great
1.5	What is the extent of the contribution to improvement of the therapy/product/method from this concrete experiment?	Minor	Moderate	Great
1.6	What is your estimation of chance of success?	Minor	Moderate	Great
1.7	Is the animal model extrapolatable?	Insufficient		Sufficient
2	***Broader social significance (short or medium term)***			
2.1	Is the research directed at replacement, reduction or refinement of animal experiments?	Not much		Substantial
2.2	What contribution to the improvement of health or nutrition of man or animal do you expect?	Minor	Moderate	Great
2.3	What is your estimation of the chance of success?	Minor	Moderate	Great
2.4	Is the animal model extrapolatable?	Insufficient		Sufficient
3	**Judgement**			
	Significance of animal experiment	Minor	Moderate	Great

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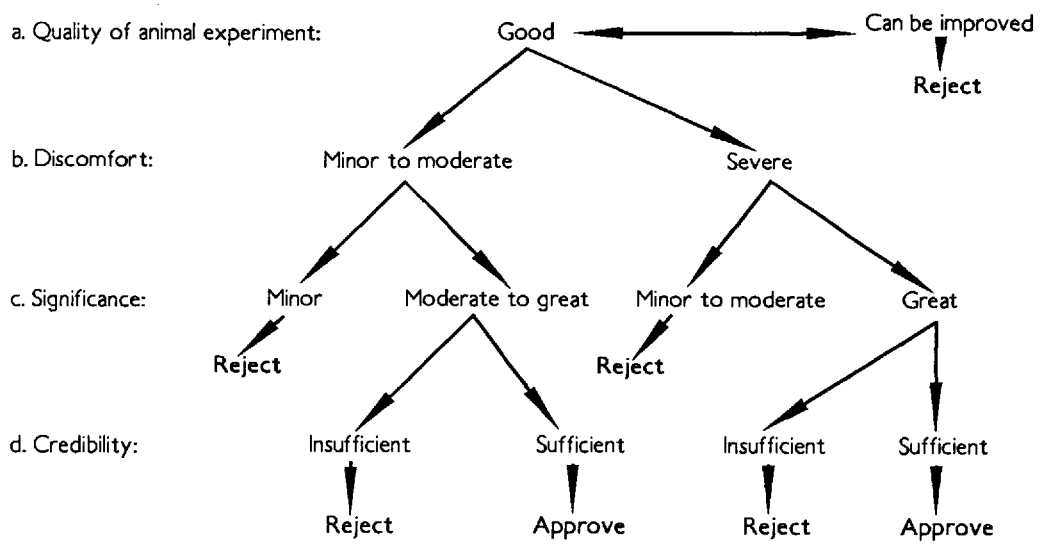
Cf	**BASIC SCIENTIFIC RESEARCH (Research into biological functions, biological processes and behaviour)**			
1	**Scientific significance**			
1.1	How great is the scientific significance of the knowledge or the insight?	Minor	Moderate	Great
1.2	What is the estimation of the scientific quality?	Minor	Moderate	Great
1.3	How is the scientific context of the research project?	Insufficient		Sufficient
1.4	What is your estimation of the chance of success	Minor	Moderate	Great
1.5	Does the concrete research fit in with the research project?	No	N/A	Yes
2	**Judgement**			
	Significance of the animal experiment	Minor	Moderate	Great
D	**CREDIBILITY of the group/researchers**			
1	**Group/researchers**			
1.1	Is the subject new to the group?	Yes		No
1.2	Does the group often conduct pilot studies only?	Yes	N/A	No
1.3	Is this type of animal experiment new to the group?	Yes		No
1.4	Do all members have sufficient experience with these animal experiments?	No		Yes
1.5	Does the group develop alternatives on its own or does the group participate in validity research?	–		Yes
1.6	Do the researchers have/create sufficient opportunities to look for alternatives?	No		Yes
2	**Judgement**			
	Credibility of the group/researchers	Insufficient		Good
	Arguments in favour of rejection			
E	**Assessment**			
1	**Model (please circle the chosen answer)**			



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2	**Which of the questions A to D were the deciding factors?**
3	**Recommendation (circle the chosen answer)**
	a. No conclusion, because additional information is required about:
	b. Approve
	c. Approve under condition(s)
	d. Reject, but a modified proposal can be made
	e. Reject

Use of the form

The form consists of a questionnaire (*A - D*) and an assessment procedure (*E*). The questionnaire contains all questions that can be relevant for the testing of an animal experiment. In actual practice, however, each question will not have the same relevance for each animal experiment.

The questionnaire can be used as follows: at every new experiment members of the Animal Experimentation Committee go through the form and indicate which questions may possibly be problematic to the AEC. These questions are under discussion in a plenary session of the AEC. The AEC gives the opportunity to the researcher responsible to amplify on these questions. Next the AEC forms an opinion about the application, following the procedure, described under *E*. In many cases testing may be marginal. For instance, long-term projects, which have been fully discussed and about which there are no new data available, do not require to be discussed in great detail every time. Once a year or every six months would be sufficient. The questionnaire is structured in such a way that the answers on the far right side of the form contribute to approval of the animal experiment and the answers on the far left side may form a reason to disapprove of the animal experiment.

At the formation of a judgement four types of problems arise:

- The questionnaire allows for a restricted number of answer-categories (in some cases only two). The AEC will have to indicate which answer mostly accords with the AEC's opinion, so that AEC is requested to give a clear judgment (eg sufficient of insufficient).
- With cluster *C* there may be some doubt about which cluster of questions have to be answered, eg *Cp*-problem-oriented research or *Cf*-fundamental scientific research. It is not the intention that the judgement about two clusters is added up: twice a moderate judgement do not make a research very important. The AEC has to work out where the main significance of the research lies.
- The AEC itself has to decide how heavy unsatisfactory aspects of the research will weigh in its judgement. This means that the AEC has to develop jurisprudence, both within its own institution and in dialogue with other AECs.
- An AEC has to strive for consensus, but this does not guarantee that it will always arrive at a uniform point of view. For these cases (and as long as no legal regulations exist) the AEC will either have to develop a process of decision, or refer the research to the license or seek the advice of the Advice Committee (sect 18).

Explanation of the questionnaire

A1.1 As a rule judgement of the scientific quality is not considered as being a task for the AEC. Consequently this judgement has to be made elsewhere. This can be done, for instance, by asking the approval of a statistician.

A1.2 In all cases the researcher has to give a statistical account for the number of animals used.

A1.3 Doing a pilot study may lead to an improved experimental design.

A1.4 Prohibited (EC directions) unless the animal has recovered and unless, for the next experiment, the animal is totally anaesthetized and will not awake, unless it is only a matter of minor discomfort at the next experiment.

A2.1 Remember ATLA and data base-in-advancement at Proefdierkunde (Utrecht).

A2.2 Remember models without animals, with biological materials (tissues, organs), with lower animal species and research with humans (epidemiological research).

A3.1 At this point it is not only a matter of statistical justification, but also of the question wether a different experiment-planning is possible.

A4.2 WOD sect. 13, par. 1

A4.3 WOD sect. 13, par. 2

A4.4 Background of the improvement of the quality of animal experiments is always the decrease of discomfort.

A4.5 Remember the opportunities to withdraw; adapted accommodation; social contact with familiar species and diversion (enrichment, improvement).

***B* In general**

- The question of animal experimentation only arises when the animals experience discomfort (WOD sect. 1).
- When answering these questions it is advisable to make a distinction between more and less 'sensitive' animal species, and between more and less social animal species. The discomfort of a specific operation differ widely for different animal species (e.g. guppy and anthropoid).
- Because not always is being worked with one experimental group and one control group, but often worked with several groups, the questionnaire mentions experimental groups 1 to 4, meaning groups with a different treatment each.

B1.1, 1.3, 1.5, 1.7 The question is to estimate the extent of the discomfort. For this estimation one can use the information from the section animal experimentation of the VHI in the explanation of the 'Registration animal experiments and experimental animals' and of the general rule that one must assume that, when animals are exposed to certain procedures, they experience a comparable discomfort to humans, unless the opposite is proven. One must take into account that the extent of discomfort can also be determined by the frequency of the operation.

B1.2, 1.4, 1.6, 1.8 The seriousness of the discomfort also depends on the duration of the discomfort.

B2 The living conditions and, in particular, housing influence the well-being of the animals. The AEC will have to indicate to what extent living conditions contribute to the total discomfort of the experimental animals.

***C* In general**

- The law permits an experiment either in case of a direct or indirect significance regarding health or nutrition of man or animal, or in case of answering a scientific question. Other reasons for animals experiments are only allowed after explicit exemption from the Ministry of WVC (WOD sect. 1 and 2).
- Per animal experiment only one of the clusters of questions (*Cr, Cd, Ce, Cp* or *Cf*) need to be answered.

Cr This question makes a distinction between the importance of the animal-experiment and the significance of a product. The former case refers to the production, quality or safety of a substance. The second case to the significance of the substance itself. (eg the importance of testing the safety of a 'new' cleaning product and the significance of the cleaning product itself).

Cd More and more alternatives for diagnostic purposes are available. However, there is an increase of animal-use with regard to the production of monoclonal antibodies for diagnostics. To determine the significance of the experiment the medical or veterinary need must be judged.

Ce For education as well the standard must be that an animal experiment must be of direct or indirect significance for the health or nutrition of man or animal. This means that an animal experiment can only be permitted to students, of whom it is certain that they will perform similar actions with animals in their future profession.

Cp.1.1* and *1.2 These questions are to help assessing the urgency of the problem. The question is to indicate an opinion about the importance of solving this problem.

Cp.1.3 The question about the high-risk group is asked because:

- some diseases, eg influenza, are not serious as a rule, but for specific groups of people (CARA-patients and the elderly) they are a potential fatal disease.
- some diseases are avoidable, because with humans they are caused by their own behaviour (eg sports injury) or by poor working conditions or - with regard to animals - by human acts (defects caused by improper housing or as a result from breeding programmes).

Cp.1.6 **and** *2.3* To what extent are there well-founded expectations that the research will produce the desired results?

Cp.1.7 **and** *2.4* The extrapolatability of the animal experiment depends on the question to what extent the disease develops in the same way in animals as in humans and/or to what extent the animal functions in a comparable way to the human, on the ground of build, metabolism or behaviour.

Cf In this research a scientific question is the central point. Now the AEC has to judge the scientific significance of the research and has to estimate the possibility of a solution.

Cf.1.1 What does the research produce with regard to breaking new ground in knowledge or insight?

Cf.1.2 What estimation of the scientific quality has been made by a research committee or other official? If this did not take place, what is the estimation of the AEC?

Cf.1.3 Is the research-project part of a scientifically evaluated collaboration (EC, NWO, conditional financing, etc)?

Cf.1.4 To what extent is this a realistic project with a well-founded research-hypothesis?

Cf.1.5 To what extent does the concrete research fit in with the research project? To what extent is it a matter of an interesting, but not very relevant sideline?

***D* in general**

- It is best to answer these questions in consultation with the authority on experimental animals; for he/she is the person who has a reasonable amount of insight regarding the activities of the group. All questions **together** form a picture of the care exercised by the group and the researchers in handling animal experiments and, consequently, the animals. The AEC can allow more credit to a researcher or a research group as its trust in the careful handling of animals grows.

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