Evaluating the ethical acceptability of animal research

Henriëtte J. Bout, MSc[1], J. Martje Fentener van Vlissingen, DVM, PhD, Dip ECLAM[2] & Edgar D. Karssing, PhD[3]

The ethical acceptability of animal research is typically evaluated on a case-by-case basis. Legislation such as Directive 2010/63/EU on the protection of animals used for scientific purposes provides guidance for ethical evaluation of animal use proposals but does not dictate the outcome, leaving this determination to the ethical review committees of individual institutions. The authors assess different ethics models and how these are reflected in the guidelines of Directive 2010/63/EU. They also describe a matrix for carrying out harm–benefit analyses of animal use proposals, which they identified by examining the practices of three ethical review committees in the Netherlands. Finally, they discuss how this matrix can be applied by ethical review committees at other institutions.

The use of animals in biomedical research has led to important medical advances but presents ethical concerns among scientists as well as the public[1]. The need to respect all living creatures competes with the importance of human health and the value of scientific knowledge. Finding a balance between these factors is a task that often falls to the committees that review individual proposals for the use of animals in research. In the European Union, Directive 2010/63/EU[2] addresses the protection of animals used for scientific purposes. Directive 2010/63/EU does not attempt to answer the question of when animal research is ethically acceptable but does provide statutory guidance prescribing that proposed projects must be evaluated by different experts and that the evaluation must include a harm–benefit analysis. The outcome of the evaluation of each project will depend on specific details that differ from one case to the next. Therefore, it is appropriate for legislation to offer room for the committee to make its ethical judgment.

ETHICAL FOCUS OF THE DIRECTIVE

Although Directive 2010/63/EU does not dictate the outcome of the ethical review of animal use proposals, we can examine its prescriptions in the context of different ethical models in order to appreciate its ethical focus.

Recital 12 of the preamble of Directive 2010/63/EU[2] states, "Animals have an intrinsic value which must be respected. There are also the ethical concerns of the general public as regards the use of animals in procedures. Therefore, animals should always be treated as sentient creatures and their use in procedures should be restricted to areas which may ultimately benefit human or animal health, or the environment." These statements are in keeping with the philosophical viewpoint of zoocentrism, in which people have obligations to all sentient creatures.

In Article 5, Directive 2010/63/EU restricts the use of animals in research to a set of specific purposes[2], and in Recital 39 of the preamble, it states that "[t]he likely harm to the animal should be balanced against the expected benefits of the project."[2]. These statements align with a utilitarian approach to determining whether an act is ethical. The utilitarian approach focuses on the consequences of an act, arguing that the act is acceptable if its overall consequences are beneficial. Thus, in a utilitarian approach, the aim may justify the means.

ETHICAL REVIEW COMMITTEES IN PRACTICE

Each ethical review committee has its own dynamics and characteristics as the committee members balance

[1]University of Amsterdam, Amsterdam, the Netherlands. [2]Erasmus University Medical Center, Rotterdam, the Netherlands. [3]Nyenrode Business Universiteit, Breukelen, the Netherlands. Correspondence should be addressed to H.J.B. (h.j.bout@uva.nl).

relevant facts and arguments in a collective process that results in an ethical judgment about a specific case. It is important that this process be safeguarded to prevent it from becoming merely an exercise in paperwork. Brown, a contemporary philosopher who has published several studies on ethical reflections in organizations, describes how this can be done by formalizing the right of the committee members to receive information and to speak freely[3]. Brown stresses that all relevant stakeholders should become involved in the decision-making process, either directly or indirectly, in order to maintain an open and productive debate. Inclusion of a broad group of stakeholders in the process of ethical judgment affords the process greater force. Directive 2010/63/EU prescribes the presence of technical experts, animal welfare experts and researchers in the discussion[2] but does not mention professional ethicists or members of societal stakeholder groups. Ideally, other members of the committee can bring the arguments of these two groups into the discussion, but in reality this is not likely to happen.

Toulmin, a contemporary philosopher who worked as a staff member with the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was created in 1974 and was the first public national body to shape bioethics policy in the US, describes his experience with this commission[4]: "…many onlookers assumed that its discussions would generate into a Babel of rival opinions. (…) But things did not work out that way. (…) In almost every case they came close to agreement even about quite detailed recommendations. (…) Babel set in only afterwards. When the eleven individual commissioners asked themselves what 'principles' underlay and supposedly justified their adhesion to the consensus, each of them answered in his or her own way: the Catholics appealed to Catholic principles, the humanists to humanist principles, and so on. They could agree; they could agree what they were agreeing about; but, apparently, they could not agree why they agreed about it." Similarly interesting discussions should be predicted to take place among the members of ethical review committees.

In The Netherlands, a tradition exists of consistent and systematic evaluation of proposals for animal research. Since 1977, when the first Dutch legislation on animal welfare in research was established, several ethical committees have been formed by professional institutions and companies in the field of scientific research and have included professional ethicists. By law (amended in 1996), all research that involves animals and that poses a risk to their welfare is subject to a mandatory ethical review by a committee that advises the institution where the research is proposed to take place[5]. The collective experiences of these committees are recorded in minutes and proceedings.

We examined the ethical review process of three institutional animal use committees in the Netherlands (those of the Free University Amsterdam, the University of Amsterdam and the Academic Medical Center Amsterdam) by analyzing the minutes and proceedings from their monthly meetings from 2003 to 2013; approximately 20–30 animal use proposals were discussed during each meeting. We found that the committee members spent most of their time discussing the technical details of the proposals. They focused on the choice of animal model, the set-up of the experiment, the proper use of anesthetics and the implementation of the principles of the 3Rs: reducing the number of animals needed for the experiments, refining the experiment in order to minimize the pain and distress experienced by the animal and to enhance the animal's well-being and replacing animal-based methods with non-animal alternatives[6]. The focus on technical aspects is appropriate in order to ensure that the experimental results are compliant with scientific standards. Technical details are also aspects on which the committee members may generally agree.

However, animal research is not only a technical issue but also an ethical one. Yet we found that review committees took far less time, if any at all, to explicitly weigh ethical factors such as the intrinsic value of the animals, the benefits of the research to society and the value of the knowledge to be gained. Like Toulmin, we found that "Babel set in" when it came time for committee members to explain why the proposed experiments were ethically acceptable. Although they intuitively and formally agreed that the use of animals, and the resulting harm to the animals, should be balanced against the benefits of the experiments, they seemed to find it difficult to substantiate this perspective in the context of any specific proposal.

HARM–BENEFIT ANALYSIS MODELS

Much has been written about different models that can be used to weigh the harms and benefits of proposed animal research projects[7–11]. For example, procedural models suggest which relevant aspects should be checked in order to justify animal research, such as the legal prerequisites, the purpose of the experiments, the quality of the scientific design, the possible harm to the animals and the number of animals involved. These models offer the advantage of addressing all the ethically relevant factors. Normative models, conversely, aim to standardize the outcome of the ethical judgment. Committee members assign point values to the ethical aspects involved in the experiment (e.g., animal species, number of animals, harm, duration of the experiment, care, type of research, the research group's track record, scientific evaluation of the proposal) and then sum up the assigned points to arrive at a total for the experiment; a greater number of total points indicates a more

ethically onerous experiment. An advantage of normative models is that they objectify ethical judgments and render them suitable for comparison. But the biggest disadvantage of normative models is the suggestion that the process of ethical judgment is simply a technical matter in which committee members' ethical intuitions or personal considerations carry little weight.

The European Commission's Expert Working Group for Project Evaluation and Retrospective Assessment[12] suggests using a harm–benefit analysis model called the 'Bateson cube'[7], which combines features of procedural and normative models by prescribing both procedural aspects and specific normative principles that should be balanced. Bateson suggests balancing three different aspects in harm–benefit analyses: the benefits of the proposed research, the harm to the animals and the likelihood of achieving the benefit. The ideal research study should have high value, be of high quality and cause minimal harm to the experimental animals[13].

A MATRIX FOR HARM–BENEFIT ANALYSIS

We propose a matrix for harm–benefit analyses that is based on the Bateson cube but calls for greater precision in assessing the harm caused to the animals and the benefits presented by the research[14]. Our proposed matrix treats the likelihood of achieving the benefits not as part of the weighing process in the harm–benefit analysis but instead as a prerequisite: if the animal use proposal has insufficient likelihood of achieving the benefit, then the outcome of the ethical review must be negative, rendering a further harm–benefit analysis unnecessary. The Expert Working Group for Project Evaluation and Retrospective Assessment addresses this aspect in a somewhat technical manner by considering the appropriateness of the animal models, the quality of the arguments used by the applicant and the confidence in a culture of care at the establishment where the work will be conducted[12].

Assessing harm

The expected harm to animals should be assessed in a meaningful way. Directive 2010/63/EU[2] acknowledges different levels of harm to animals involved in experiments: mild, moderate and severe, as well as 'non-recovery'. Much has been written about criteria for assessing mild, moderate or severe harm[15], and the animal research community is close to reaching consensus on many aspects of harm assessment.

Assessing benefit

The notion of 'benefit' is quite broad, and breaking it down into more specific categories is recommended in order to assess individual projects. Directive 2010/63/EU describes seven purposes of research where the use of animals may be proposed: basic research; translational or applied research; testing of drugs, food and substances; protection of the environment; preservation of species; forensic research; and the training of professional skills[2]. It may be useful to categorize these as scientific benefits (those associated with greater scientific insight) and societal benefits (those associated with the application of knowledge, such as medical advances, environmental protection, preservation of species, forensic research and training of professional skills), although in practice this distinction may not be so clear. Ethical review committees can then determine whether the potential scientific and societal benefits of a specific animal experiment are high, moderate or low. For example, to assess the potential societal benefit of a proposed study, committee members might discuss the possible benefit to human health. Does the study address a health problem that affects small or large numbers of patients? Does it concern a local or a global issue? Is it innovative, front-line science likely to be published in a prestigious journal? Will it have any immediate or future application? Assessing potential benefit is a subjective and challenging task, and ethical committees frequently struggle with grading potential scientific and societal benefit as high, moderate or low. Thus, whereas we might be close to reaching consensus on the assessment of harm, the debate about the assessment of benefit has only just begun.

Balancing harm and benefit

After assessing the degree of harm and the potential scientific and societal benefits of the animal experiment, the ethics committee balances these factors to determine whether the proposed research is acceptable. Not all scientific work is equally valuable, and hence the use of animals is not acceptable in every case. Instead, the degree of harm must be justified in relation to the proposed benefit.

Our matrix illustrates the balance between different levels of harm and different levels of benefit (**Fig. 1**). For basic research with great scientific benefit

			Harm		
Benefit	Scientific	Societal	Mild	Moderate	Severe
	Low	Low			
		Moderate			
		High			
	Moderate	Low			
		Moderate			
		High			
	High	Low			
		Moderate			
		High			

FIGURE 1 | A harm–benefit analysis matrix, illustrating the balance between harm to the animals involved in a study and potential scientific and societal benefits of the study. Cases in which the degree of harm is justified by the potential scientific and societal benefits are shaded green, whereas cases in which the degree of harm is not justified by the potential scientific and societal benefits are shaded red.

but no reasonable expectation of near-term (e.g., within 20 years) applicability, no more than moderate harm is acceptable. A high degree of harm can be accepted only if both the scientific and the societal benefits are high.

APPLYING THE MATRIX DURING ETHICAL REVIEW

The matrix should not be construed as a statutory framework. It is not a prescriptive tool but rather a descriptive illustration of how the harm–benefit analysis is often carried out in the ethical review committees that we observed. We hope that it will serve to enhance the ethical debate surrounding the justification of animal use in science. In our experience, this matrix facilitates dialogue between the members of the committee and the researchers during ethical review of animal use proposals. As part of the harm–benefit analysis, committee members might ask the researchers whether it is possible to reduce the degree of harm caused to the animals by redesigning the proposal or whether there is a potential societal benefit that should be addressed in the proposal. In turn, the committee members themselves might be asked whether it is appropriate to depart from the line of thought proposed by this matrix in a specific situation and, if so, what are the ethical or other reasons for such a departure.

ADVANTAGES AND LIMITATIONS OF THE MATRIX

Our matrix combines aspects of both normative and procedural models of harm–benefit analysis: it makes ethical reasoning explicit so that the resulting judgments are consistent, realistic and explainable to others. The main advantage of working with this matrix is that it enhances communication, in part by generating vocabulary and focus for the evaluation of animal use proposals and for discussion of this process both among committee members and between the committee and the researchers involved. The matrix can help researchers and committee members alike to describe the benefits of research more explicitly. Yet application of this matrix has its limitations, particularly in the assessment of scientific and societal benefits. It also does not address the ethics of animal research or research in general. The matrix merely describes how ethical evaluation of animal use proposals is done in practice.

CONCLUSIONS

Directive 2010/63/EU provides guidance for the ethical evaluation of the proposed use of animals in research by institutional review committees and indicates that this evaluation should include harm–benefit analyses, but it does not provide a detailed scheme for these analyses. We examined the practices of three ethical review committees in the Netherlands over a period of 10 years and developed a matrix that describes how these committees carry out harm–benefit analyses. The matrix aims to balance the harm caused to animals in a proposed study with the potential scientific and societal benefits of the research to help committees determine when animal research is ethically acceptable. Applying the matrix to the ethical evaluation process can help to improve this process by making it more consistent.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

Received 31 March 2014; accepted 29 May 2014
Published online at http://www.labanimal.com/

1. Franco, N.H. Animal experiments in biomedical research: a historical perspective. *Animals* **3,** 238–273 (2013).
2. European Union. Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. *Official Journal of the European Union* **L276,** 33–79 (2010).
3. Brown, M.T. *Working Ethics: Strategies for Decision Making and Organizational Responsibility* (Jossey-Bass Inc., San Francisco, 1990).
4. Toulmin, S. The tyranny of principles. *The Hastings Center Report* **11,** 31–39 (1981).
5. Wet op de dierproeven 12 September 2014. ⟨http://wetten.overheid.nl/BWBR0003081/geldigheidsdatum_12-09-2014⟩.
6. Russell, W.M.S. & Burch, R.L. *The Principles of Humane Experimental Technique* (Methuen, London, 1959).
7. Bateson, P. When to experiment on animals. *New Scientist* **109,** 30–32 (1986).
8. Theune, E. & de Cock Buning, T. Grenzen aan dierexperimenteel onderzoek: toetsingsprocedure. *Proefdier en Wetenschap* vol. 4 (Rijksuniversiteit Leiden, Leiden, the Netherlands, 1991).
9. Porter, D.G. Ethical scores for animal experiments. *Nature* **356,** 101–102 (1992).
10. Stafleu, F.R., Tramper, R., Vorstenbosch, J. & Joles, J.A. The ethical acceptability of animal experiments: proposal for a system to support decision-making. *Lab. Anim.* **33,** 295–303 (1999).
11. Voipio, H-M., Hirsjarvi, P., Ritskes-Hoitinga, M. & Nevalainen, T. in *Proceedings of 9th FELASA Symposium: 4–17 June 2004, Nantes, France* (eds. Gamble, M.R. & Millington, S.) 60–62 (Laboratory Animals Ltd., London, 2004).
12. European Union. National Competent Authorities for the implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes. A working document on Project Evaluation and Retrospective Assessment. 18–19 September 2013, Brussels, Belgium.
13. Innes, C.C. Ethical regulation and animal science: why animal behaviour is not so special. *Anim. Behav.* **74,** 15e22 (2007).
14. Bout, H.J. in *De Weging Gewogen: Beschouwingen Over Ethiek en Dierproeven* (eds. Swart, J., Jonker, M. & Tramper, R.) 79–87 (DAMON, Budel, the Netherlands, 2009).
15. Directive 2010/63 Annex VIII; COMMISSION IMPLEMENTING DECISION of 14 November 2012: establishing a common format for the submission of the information pursuant to Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes (2012/707/EU).