DISCUSSION

Turning Apples into Oranges? The Harm-Benefit Analysis and How to Take Ethical Considerations into Account

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How can expected study benefits and animal harms be weighed against each other? What is the unit and common currency that allows this weighing to be performed?

Suppose you are a scientist, working in the field of oncology and using live animals in your studies. Furthermore, suppose you have an excellent track record, you are well respected in the research community, and you regularly publish in high-ranking journals. One day, a person that you have not met before, wants to see you and talk about your work. Despite the fact that your time is extremely scarce, you invite this very person to your office and postpone your work on a follow-up research proposal. It turns out that the person who wants to talk to you is a member of a major animal protection group. She asks you the following question: "I came across a project summary, published according to Article 43 of *Directive 2010/63/EU*. Knowing your research, I think it is your project. Can you ethically justify the use of animals in your work? What I mean is: Do the benefits really outweigh the harms? And which ethical considerations do you take into account?" The animal protectionist is actually asking something for which you should, in fact, be well prepared. *Directive 2010/63/EU*[1] was transposed into the national laws of the EU Member States. In Article 38(2) of the Directive, it is emphasised that a harm–benefit analysis of any project involving the use of animals must be carried out, in order to assess whether the harms related to the project are outweighed by the expected benefits. Furthermore, the relevant passage stipulates that *ethical considerations* have to be taken into account in this assessment (emphasis added by the current author):

"The project evaluation shall consist in particular of the following: d) a harm–benefit analysis of the project, to assess whether the harm to the animals in terms of suffering, pain and distress, is justified by the expected outcome *taking into account ethical considerations*, and may ultimately benefit human beings, animals or the environment."

Consequently, the question arises as to how the harm–benefit analysis can be carried out, and how the term "*taking into account ethical considerations*" might be understood in this context. The meaning of this term is of major importance, since it provides a legally binding basis for the approval or rejection of projects. In other words, everyone who aims to secure the authorisation of a project in the EU has to make sure that the expected benefits outweigh the harms, and the justification must take into account ethical considerations, whatever that in fact means. All this has to be done on legal grounds — it is not just some fancy idea of animal protectionists.

The harm-benefit analysis: A challenge or mission impossible?

At present, and to my knowledge, it is not at all clear how to prove, in a transparent and objective manner, that the expected benefits of an experimental study outweigh the expected harm to the animals to be used. Moreover, the actual meaning of the term "ethical considerations" remains vague, to say the least. How can expected study benefits and animal harms be weighed against each other? What is the unit and common currency that allows this weighing to be performed? And can 'ethics' help to turn apples into oranges, so that only comparable weights are on the scales? Since the Directive does not provide any specifications on standards for the harm–benefit analysis and how to take ethical considerations into account, the passage invites the reader to speculate.

The working document on *Project Evaluation and Retrospective Assessment* (WD 2013),[2] from September 2013, is only of limited help. It provides important criteria and ideas, but it leaves the reader without help when it comes to a methodology for transparent decision-making. It refers to the *Bateson Cube*, which indicates what should be taken into account, but whether its dimensions (i.e. benefit, likelihood of benefit, harm to animals) are ethical in nature, and whether these dimensions are sufficient for the harm–benefit analysis, remains open to question. Furthermore, no measure is provided to allow

the various dimensions to be made comparable. Take, for example, 'benefit'. Here, a set of analytic questions is given (WD 2013, p. 21):

What will be the benefits of the work?

Who will benefit from the work?

How will they benefit/impact?

When (where possible) will the benefits be achieved?

But, even if we had the answers to all these questions, how can they be integrated in the harm-benefit analysis? Does this mean that there should be no research on orphan diseases, because only few people can benefit? Does it mean that it matters who benefits in terms of age? Does this mean that a new cold remedy is more important than a new cancer treatment, since many more people will use it and it therefore has a greater impact? Is research more important, if it will bring about practical benefits sooner, and should this influence the harm-benefit analysis?

Similar questions arise on the harm side. Is the severity classification enough? Shall we add all harms done to individual animals, and if so, how do we deal with harms that are related to the project indirectly, such as harm to animals that were necessary to establish the particular mouse strain used? Is the absolute number of animals used in an experiment something that should be taken into account — or is it acceptable to adhere to the Three Rs criterion of *reduction*, and to use the minimum number of animals? And if the absolute number should count, what is a 'high' number (100 dogs, or 12,000 mice?) and does 'high' vary, depending on the research field in question? And if we knew all that and more, how could we bring all these criteria into one methodology, in order to carry out a transparent harm-benefit analysis? At the moment, this seems to be a mission impossible, rather than a challenge to be dealt with.

Steps to tackle the problem: Criteria, methodologies and committees

One could of course go on and on with this list of open questions. In order to answer at least some of them, researchers from various fields — and in particular, ethicists — try to take on the challenge. For example, the Messerli Research Institute (Vienna, Austria) hosted an international symposium in March 2013, in order to discuss possible steps toward overcoming the aforementioned problems. A conference on the harm-benefit analysis was also held in Bergen in 2014, and we debated the issues at the W*orld Congress on Alternatives and Animal Use in the Life Sciences*, held in Prague in late 2014. Many well-known experts in the field of ethical evaluation of animal experiments took part. At all these meetings, the aim was to bring together state-of-the-art knowledge with regard to the issues. For example, in Vienna, 22 speakers from eight European countries and the USA discussed their experiences and the current situation surrounding these issues in their respective countries. The lively discussions went to show that many challenges remain, but some issues can be solved.

In the course of the Vienna symposium, not only the criteria and aspects that should go into the harm-benefit analyses were debated. Importantly, different methodologies such as checklists, scoring systems or comparative methodologies, were also introduced. Most of the experts emphasised the importance of independent and well-balanced committees, and the integration of lay people (i.e. non-specialists) and representatives of animal welfare organisations into these committees. Taking into account the lay people's perspectives and current public opinion would contribute to an up-to-date ethical evaluation of animal experiments. But, by taking all of these factors into account, are we any way nearer solving the problem of how to transparently weigh apples against oranges successfully?

Although no 'super-theory' to resolve all of the issues was identified, the challenges became much clearer. Furthermore, things to be avoided came to the table: A particular and major threat that has to be avoided when developing methodologies for the harm-benefit analysis became very clear, and that is over-bureaucratisation. Any methodology for the harm-benefit analysis has to be a user-friendly tool that leads to deeper reflection on individual animal experiments. The different forms of methodologies were summarised in the following three groups:

- comparative methodologies that use positive lists (white-lists) and negative lists (black-lists) of animal experiments, in order to evaluate the project in question;
- scoring strategies that quantify the extent to which relevant criteria are met, and that provide an algorithm for calculating the harms and benefits of projects; and
- check lists that provide binary (yes/no) evaluation methods, e.g. in the form of decision trees.

Whether these methods are used within or without the committee structure makes a big difference, and both scenarios are indeed possible. Ideally, applicants should follow a structured procedure and provide the relevant information according to a set of clear standards and criteria that have to be met. Interdisciplinary committees would then be able to evaluate the projects according to the same standards and criteria. These evaluations could inform the competent authority's decisions.

Many things could be said, and indeed have been said in the past, about methodologies, and a great deal has also been written on the subject. Needless to say, we did not come to any final conclusions at the symposium in Vienna, nor in Prague, nor in Bergen, on this complex but vital matter.

How to proceed from here?

In order to reach a clearer vision of how the harm-benefit analysis can be brought into a feasible

methodology, any ideas are welcome. Exchanging ideas and arguments might inspire and boost the debate. This short article serves as an open invitation to all interested experts in the field to start such a debate. Since this should happen in a focused way, the following topics might be useful to guide the discussion:

- *Committees and their limitations and advantages:* A great number of EU Member States have established local and national committees to support the authorities in decision-making on submitted proposals. Certainly, such committees have the advantage of bringing skilled experts from the sciences, statisticians, representatives of animal protection groups and lay people, to work together in order to formulate a statement on harms and expected benefits. However, these committees often work without explicit methodology or criteria. So the question arises as to how they can safeguard transparent and non-arbitrary decision-making when they carry out harm–benefit analyses. I am sure that many of the readers are experienced members of such committees, and it would be very useful, if they would contribute with their experience, knowledge and ideas.
- *Methodologies*: It would be of great interest to share knowledge on the advantages and disadvantages of methods used. If committees and the national authorities apply consistent methods and explicit criteria, it would be of utmost importance to get into an exchange of views and experience on whether and how such methods can support and improve the decision-making process.
- *Ethics and Law*: A third question relates to the terminology used in the Directive. If ethical considerations should be taken into account, should these considerations exceed existing law or is "ethics" to be understood within legal limits (and is not allowed to exceed existing law)? Here, ethics runs the risk of contradicting the principle of legality in constitutional states. In other words: How is the term "taking ethical considerations into account" interpreted in different countries. It would be great to get some insight into this.
- *Experience from the past*: Generally, since many countries have carried out harm–benefit analyses in the past, knowledge of their experiences could contribute to future developments.
- *Ideas for the future*: Finally, a possible thought experiment is to think about where we are going to be in 20 years' time. How will the debate look in 2035? Will we still be trying to weigh apples against oranges?

These questions and statements aim to initiate a debate that is relevant to all EU Member States and everybody involved in animal research. It would be very useful, if experts in this forum were willing to find some time to contribute to a lively and future-oriented discussion, in order to solve at least some of the open questions mentioned above. The idea is to continue to build up knowledge on the process of harm–benefit analysis in animal research, and maybe improve the situation for both animals and researchers. Perhaps this forum could bring us closer to the point where researchers were able to respond to the question as to whether, and indeed which, projects involving live animals are justifiable, and which are not. Being able to respond to the question as to whether a project is worth carrying out or not, could demonstrate that scientists are able to take on this responsibility in a knowledge-based society and thus can contribute to ethical welfare.

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[2]Anon. (2013). *National Competent Authorities for the Implementation of* Directive 2010/63/EU *on the Protection of Animals Used for Scientific Purposes. Working Document on Project Evaluation and Retrospective Assessment*, 42pp. Brussels, Belgium: European Commission.