

SUMMARY

Report on the consensus meeting between Stakeholder platforms in Europe in the context of *ecopa*/CONAM.

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Introduction

According to the European Union (EU) policy Directive 86/609/EEC the member states of the EU are required to stimulate the development of alternatives for animal experiments and enforcing the acceptance of alternatives in experimental practice, also called the '3Rs-strategy'. Central elements in the 3Rs-strategy are: *Reduction*, *Refinement* and *Replacement*.

The *ecopa* (European consensus-platform for (3R)-alternatives) and the EU CONAM project (Consensus Networking on Alternative Methods) were established to maximize results and minimize conflicts within this 3Rs-strategy and at the same time striving for consensus between all stakeholders and member states involved. As an umbrella organization for all National Consensus Platforms (NCP) in the EU, *ecopa* subscribed the proposal of the working group on Ethics at the annual meeting in November 2003, to unite in a workshop all the stakeholder members of the national Platforms and to initiate among them a process of mutual learning and mutual understanding regarding basic values behind the 3Rs policy. The organization of this workshop was executed in spring 2005 in the context of the EU Framework VI, CONAM program, workpackage IV: Harmonization ethical investment (coordinator Prof Tjard de Cock Buning).

The focus was chosen to discuss values and norms on two topics: 1) pain and suffering of animals and 2) the status of animals. Finally, due to a balanced co-funding by industry, Animal Welfare organizations and scientific/governmental bodies 27 participants from 11 different NCPs attended the meeting. The group of participants consisted of stakeholder experts from industry, academia, animal welfare and governmental institutions. The meeting took place in Ljubljana, Slovenia from the 10th till the 12th of June 2005 and this report describes the results of that meeting.

On the first and second day the dialogue workshops took place. The workshops were designed according to the focus group method and are further discussed below. The national delegates were mixed in three dialogue-groups of 8-11 participants from the various countries, but in such a setting that the stakeholders were equally balanced. The two topics were discussed under supervision of three skilled moderators. Shared values and areas of consensus and dissensus were explored in an inspiring context. In addition the participants filled out questionnaires before and after the meeting in order to evaluate the efficacy of the consensus meeting as a tool in reaching consensus. Besides that, the questionnaires served as a way to obtain individual data on the two themes being discussed. The third day was dedicated to a discussion on the various ways NCPs choose their policy goals and how they organized their activities and the way different stakeholders managed to contribute to the three Rs. Practical knowledge was also exchanged between older and newer NCPs. This resulted in an overview of the different NCPs and their achievements in managing the platforms over the years.

The results can be regarded as the state of the art description of the opinions on the subject of pain and suffering and status of animals within the EU by professional stakeholders, at the same time indicating areas of consensus and dissensus. The expectation is that this meeting can contribute to the process of mutual understanding and harmonization of the 3R strategy in an expanding Europe.

The 3R principle

The structure in which alternatives to animal research are being developed is known as the three Rs. The three Rs stand for **Reduction** of the number of animal experiments, **Refinement** of the way in which animals are used in experiments and the experiments are applied to the animals, and **Replacement** of animals by other means of getting the required

information.

The concept of the three Rs was first described in the book *Principles of Humane Experimental Technique*, by the authors William M. S. Russell and Rex L. Burch in 1959. The three Rs define “all procedures that can completely replace the need for animal experiments, reduce the numbers of animals required, or diminish the amount of pain and distress suffered by animals in meeting the essential needs of man and other animals.”

Reduction: This describes the way in which fewer animals are used to generate the required information. For example by statistical analysis of experimental plans BEFORE the experiments are performed. In this way scientists ensure that the smallest possible number of animals are used in a research study, while at the same time checking that enough animals will be used to give a reliable result.

Refinement: This includes all procedures that make the animals more comfortable. Among important Refinement activities are the enrichment of the cages of the animals.

Replacement: This is essentially the use of techniques that replace the use of animals entirely. A weaker form of replacement is “relative” replacement and relates to options to replace higher animals (mice) by lower animals (snails, daphnia and bacteria).

Summary

A consensus meeting was organized for all the members of the National Consensus Platforms for Alternatives that are all members of the ‘umbrella organization’ *ecopa*. 27 Participants from 11 countries were present in Ljubljana (Slovenia). The aim of the meeting was twofold. (A) To explore the level of consensus and dissensus between the national platforms and stakeholders regarding the interpretation and implication of 1) capacity for pain and suffering of (experimental) animals and 2) the status of animals in relation to Replacement. And (B) to catalyze a consensus process, among stakeholder platforms in the field of laboratory animal research, towards harmonizing the 3R strategy within Europe.

Methodology

Two approaches were used: 1) two dialogue sessions and 2) and a good-practices workshop. The subject of the first workshop was Refinement in relation to pain and suffering of test animals and the second workshop was about Replacement of test animals by ‘lower’ animals in relation to status of the animal. In order to have a productive and positive meeting as well as a structured investigation of arguments three conditions had to be met. Participants were expected: 1) to critically view their own basic assumptions, 2) to take each other serious and 3) to avoid power play. The groups were guided by a moderator and all followed the same process in which they determined ‘fields of research that were eligible for Refinement’, ‘methods of Refinement and responsible stakeholders’, ‘possible difficulties to be encountered’ and ‘solutions for these possible difficulties’. Through this process it was possible to make an inventory of current practical and ethical issues related to Refinement in relation to pain and suffering and Replacement in relation to status of the animal.

The questionnaires served as a means to investigate the participants’ individual insights on the status of animals and the capacity for pain and suffering as well as to evaluate the process of the meeting as a means to increase consensus. The questionnaires were analysed after the meeting.

On the second day one of the groups felt they could not work with the workshop method described. At that point a variation of the Socratic Dialogue Method was introduced. This is a type of dialogue method that is meant to explore a key concept that is still ambiguous. In the Socratic Dialogue Method, exploration starts with a concrete example and is normally conducted over a period of four days. In this case it was only limited to one day.

Results workshops

Day 1 - Refinement

Inventory of refinement priorities

The first step in the workshop program resulted in three areas of research that are considered by the participants as most eligible for Refinement and Replacement; these areas are: toxicology, neuroscience and animal models for human disease. The most important reasons why Refinement in these fields has priority over other fields are related to the high level of pain and suffering by the animals, and the fact that the level of pain and suffering is hard to determine, or not avoidable (for instance in neurological research where it is not possible to use analgesics). Other reasons mentioned are: the high number of animals used, the (deliberate) long duration of experiments in the field of chronic toxicity and human disease models. Participants also mentioned that some research aims are considered as invalid justifications for the severity of pain and suffering of the animal, like legally mandatory safety tests that do not yield new scientific knowledge and the questionable extrapolation of some of this regulatory tests. Suffering and death, as a consequence of not well defined endpoints in routine toxicity testing is also viewed as avoidable. In the field of neuroscience the use of animals with high neurophysiologic sensitivity (e.g. non-human primates) is an important reason to Refine, especially because non-human primates are often housed in isolation that causes suffering for these social animals.

Anticipating problems and solutions

In the next step the participants anticipated to possible problems and formulated solutions to reduce or otherwise compensate for pain and suffering in test animals. Most solutions were focused on better training, more data sharing, better risk assessments, using non-invasive techniques, improvement of housing facilities and raising public, academic and governmental awareness about alternative methods. For each specific solution a responsible stakeholder was assigned. It was regarded the task of Industry and Academia to increase the quality of laboratory animal science training. The role of Animal welfare was said to be important as social actor to sensitize public and government to increase awareness of pain assessment and alternative methods. They might have a constructive role in putting political pressure on the validation process for the acceptance of alternative methods. Government is expected to appoint inspectors and state vets, provide legislation and guidelines for testing compounds, standards for welfare monitoring, degree of suffering and establishing endpoints and regulation of data sharing. For some solutions other organizations were assigned a role, e.g. ethical committees, OECD, FELASE etc. Specific solutions for welfare problems in the field of neurosciences are e.g. the setup of a GLP/quality warranty system, expert meetings and housing of primates in groups.

Day 2 – Replacement

Although all stakeholders preferred *absolute* replacement options (= replacing animals by non-animal models). In this workshop the cultural aspects of the status of animals were explored and therefore we use the term ‘Replacement’ in the *relative* meaning of replacing higher classified animals by lower classified animals, and thus forcing the participants into the uncomfortable heart of the dilemma (Why are some animals more (un)equal than others?).

Inventory of replacement priorities

The participants selected three research fields - toxicology, neurosciences and human disease models - and discussed which animals should be replaced with high priority. Particular non-human primates, dogs, cats, hens and rabbits were discussed. Reasons given to replace these animals, were high neurophysiological sensitivity and great capacity for psychological and physical suffering. Important in this reasoning was also the social relationship with animals and the (im)practicality in handling. When investigating why non-human primates should be replaced more reasons came up, like similarity to man, evolutionary history, intelligence and self-consciousness. As replacement options were mentioned non-mammalians, human volunteers, lower primates, rats, squids, non-vertebrates and pigs.

Anticipating problems and solutions

The replacement of non-human primates with human volunteers was ideally favoured by most participants but meets several hard-to-concur difficulties like: the use of invasive techniques, absence of suitable light invasive human diagnostics, finding volunteers and the fact that society will disapprove even though people have volunteered. As general problems were mentioned finances, to change the investments in non-human primate research and attitude, like reluctance in using a different animal than a non-human primate and the historical approach/method. These hurdles to replace non-human primate research (or more general: higher animal models) were systematically discussed in relation to possible solutions to surpass these problems. The solutions for problems concerning human volunteers involved organ donation, using advanced imaging techniques, creating public acceptance through communication resources, ethical committees. For general problems the solutions are mostly focused around more funding of replacement research and stimulation of replacement methods, communication and sharing data between industry and academia to solve knowledge and attitude problems, use of well informed people to motivate government. The stakeholders were assigned different roles in solving these problems, government should be involved in regulation and stimulation of financial resources, academia and industry should do more research on replacement and Animal Welfare should create public acceptance for human volunteers. For the solution of general problems several stakeholder should take responsibility together. Researchers should receive more information and training to overcome their sceptical attitude against alternative methods.

In the final part of the workshop, participants were asked to render a ranking order with respect to the moral status of animals. Interestingly, one group used criteria such as societal/personal likes/dislikes of animals, evolution/complexity of development/animal structure, intelligence, social interaction. However, when the participants were asked to place a switch point where animals on the right symbolized animals that deserve moral concern and those on the left are animals placed not deserving moral concern. The participants, as a group,

appeared to be unable to reach consensus because they regard the combination of criteria essential for the status of animals. A second reason mentioned, was that there is not enough knowledge about a lot of lower animals and ranking is therefore impossible on biological grounds.

Socratic Dialogue Method on Replacement

On the topic of Replacement one group at first discussed the definition of relative replacement. The different definitions stated were: donating organs for *in vitro* systems; replacing a vertebrate with an invertebrate; replacing an animal regulated by law by one not regulated by law; sentient replaced by non-sentient (if possible to prove).

This group found it difficult to name two fields of research where test animals should be replaced. It was decided by the moderator to use the Socratic Dialogue Method to explore this topic further instead of the intended dialogue program. So a new question for exploration was formulated: Why should 'higher' animals be replaced by 'lower' animals?

This raised the preliminary question if the discussion should be about practical and technical reasons or about animal specific reasons. The group decided that the question was to be about the *animal* specific reasons. Continuing on the meaning of the notions 'higher' and 'lower', the criteria here mentioned were comparable with the ones in the other groups: level of consciousness, sentience and (neurological) physiology and complexity, but also evolutionary closeness to the human race. Next to these criteria, participants also agreed that the distinction between species depends on culture and there is no distinction as long as there is a possibility of pain. Also animals, it was said, have their own niche and have their own importance in that niche. On a philosophical level humans have an anthropocentric view which gives them the tendency to make a distinction between high and low, but actually it suggests that one species has more value than another, which is not true. Regarding the high/low order, consensus was reached that this order is artificial and defined by biological, legal and cultural factors, all of which are needed to form this distinction. In this context, however, the biological reason is regarded stronger because it is related to the capacity for suffering. When grading the capacity for suffering it was agreed that it is possible to talk about higher or lower, in some sense. However, at this stage, the "why question" (in "Why should 'higher' animals be replaced by 'lower' animals?") was still unanswered and deeply framed in cultural factors.

One of the main cultural determinants is that humans use animals as an instrument, while the ideal position might be to live in symbioses with the animal and nature, and respect that every animal has an intrinsic value.

But it was realized that is actually impossible to know the animal on it's own terms. At least one should work out what is estimated as less harmful for the animal. A case-by-case decision should be followed because many intricate criteria are morally relevant when deciding to replace animals for other animals. For concrete decisions, the animal species that has the least pain and suffering should be used. This might also imply that a lower animal is replaced by a higher animal.

Overall consensus was reached on:

- The term "replace" in today's context is that a "higher" animal is replaced with a "lower" animal. *Because we presume "lower" animals can suffer less.*
- One should focus on a case-by-case solutions.
- Progress is in finding the non-animal alternatives.

Results questionnaires

When rating the status of animal species and their capacity for pain and suffering, in general the participants from stakeholder categories Academia, Government and Industry (and also the four different European regions) classified the more complex animal species in a higher category than the less complex. Also the more complex species were regarded as having a higher capacity for pain and suffering than the less complex species. Mammals were classified the highest, followed by bird (chicken), fish, amphibian (frog) and lastly the invertebrates. We observed that Animal Welfare didn't make a distinction in status and capacity for pain and suffering between different animal species because they rated all species the maximum (10 points), except for the invertebrates that were classified quite a bit lower which was more in line with the other stakeholders.

In general we observed from the *after* questionnaires that in case of a **high research aim** (colon cancer) both Academia and Government found it more *acceptable* to use all animal species in experiments that cause *mild* pain than to use these species in experiments that cause *severe* pain. Industry scored in both cases *almost unacceptable* and Animal Welfare scored in both cases for most species *unacceptable* (except for nematode).

The same dataset showed that in case of a **low research aim** (hair loss for men) for all stakeholders it mattered less whether the experiment caused mild or severe pain; acceptability was considered quite low in either case except for the nematode.

Conclusions

Conclusions on the workshops

Regarding the workshop on *Refinement* it is concluded that there are two important fields of research that are eligible to Refine: '*Toxicology/safety testing*' and '*Animal models for human diseases*', the latter one including the field of '*Neurosciences*'. General reasons for Refinement include: a high level of pain, ill defined humane endpoints, bad animal well being, problematic extrapolation of results to real world problems is problematic, long duration of experiments and public and political unawareness. Subsequently it was observed that consensus was reached on a wide variety of options to Refine the two mentioned research areas (described in detail in the chapter 'Results' in the main report). Finally it was discussed which constraints/aspects are important for successful implementation of the proposed options for refinement. The following aspects were listed: data sharing, assessment of severe pain in animals, public and political unawareness, improving animal well being, attitude, education, platform influence and financial means. However, these aspects are hardly fulfilled in reality. The participants described and reflected on the possible drawbacks and corresponding solutions. The mentioned solutions can roughly be divided into three main fields: Training and education, Knowledge sharing and Communication.

Regarding the workshop on *Replacement* it was observed that there are three important fields of research that are eligible for Replacement of involved animals with 'lower' animal species: '*Toxicology/safety testing*', '*Animal models for human diseases*' and the field of '*Neurosciences*'. General reasons to Replace certain animal species in these fields include: neurological sensitivity, social interaction with humans, evolutionary history, intelligence and self-consciousness, among others. However, replacement by human volunteers or other animals is difficult because: invasive research on human volunteers is ethically prohibited to perform, society's values regarding humans, absence/costs of suitable models/methodology in case of human volunteers, regulatory obstacles, lack of financial resources and attitude problems (regarding non-human primate researchers). Again the mentioned solutions can

roughly be categorized into three main fields: Training and education, Knowledge sharing and Communication.

General conclusions on the workshops regarding consensus and dissensus

A high degree of consensus was observed between the national platforms/stakeholders regarding the two topics of Refinement and Replacement does exist. Because major disagreements on the discussed subjects didn't occur and the process' dynamic was continuously moving towards consensus, we conclude that within this specific group of Platform members significant areas of dissensus were absent, or hidden by the dialogue setting.

Conclusions based on the results of the questionnaires

All individual questionnaires showed that nematode and drosophila were scored the lowest as well in the questionnaires taken *before* as in the one taken *after* the meeting; indicating an evident distinction between vertebrates and invertebrates. This is true for the results concerning questions regarding capacity for pain and suffering as well as status. It is also true for both themes that in general all subgroups (stakeholders and regions) rank the animals in the same way.

After the meeting took place, the stakeholder categories Academia, Government and Industry thought more similar about status and capacity for pain and suffering than they did before the meeting. We conclude that this result is in line with the hypothesis that the structure of dialogue facilitates a process of consensus.

Recommendations coming from the workshop on Good practices

The inventory of the specific national context in which a National Consensus Platform operates in 2005 showed a large variety of mandates and policy goals. There is a need for the latest scientific information with respect to criteria of severity of suffering and good technical ways to organize knowledge sharing among scientist to reduce repetition of animal research. However, a central theme that all Platforms sooner or later have to manage is "communication strategy". This is important for the visibility of the Platform and its mission towards politicians, legislators, researchers, (inter)national institutions and the public at large. It was recommended that a second European meeting of the Platform members is dedicated to pragmatic options to design and implement an effective communication strategy for *ecopa* Platforms.

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