

tabula rasa

GEDRAGSVERANDERING
EN COMMUNICATIE

Systematic reviews in the laboratory animal domain

Round table meetings on the added value, opportunities, and challenges, commissioned by the Ministry of Economic Affairs

The Hague, January 2014

Christine Swankhuisen MA
Ingeborg Smit MSc, MA

Content

1	Occasion and Aim	3
1.1	Motion in the Lower House: promoting systematic reviews of animal studies as a standard	3
1.2	Aim: small-scale meetings to map out opportunities and challenges	3
2	What is a Systematic Review?	4
3	Main Conclusions	5
3.1	Many are unfamiliar with the methodology, particularly non-clinicians	5
3.2	Systematic reviews have added value but should not be made compulsory ..	5
3.3	Recommendations for stimulating systematic reviews	7
4	Results of the Round Table Meetings	8
4.1	The value of systematic reviews.....	8
4.2	The usefulness or uselessness of performing systematic reviews	11
4.3	Opportunities and challenges in practice.....	13
4.4	Stimulating systematic reviews	16
5	Policy Recommendations	19
5.1	Embedding systematic reviews in education	19
5.2	Course development	20
5.3	Stimulating the performance of systematic reviews.....	20
	References	22
	Appendix I – Participants Round Table Meetings	24

1 Occasion and Aim

1.1 Motion in the Lower House: promoting systematic reviews of animal studies as a standard

- In 2012, the Lower House passed a motion aiming to promote systematic reviews of animal studies as a standard. On 10 December 2013, a change of the Wet op de Dierproeven (Animal Experimentation Act) was accepted, bringing Dutch legislation in line with the European guidelines for '*the protection of animals used for scientific purposes*'. One of the goals of this law is to promote the 3 Rs (Refinement, Reduction, and Replacement of animal experiments). The change in the Animal Experimentation Act comprised a new motion aiming to include education in the field of systematic reviews of animal experiments in the laboratory animal science course (FELASA category C course). Systematic reviews can help to enhance the scientific quality and clinical relevance of animal studies and ease implementation of the 3 Rs (NKCA, 2013).
- With a view to performing the motion in the Lower House, the Ministry of Health, Welfare, and Sport wished to gain a better understanding of opinion on systematic reviews in the animal experimentation domain. In 2012, Tabula Rasa made an inventory by interviewing scientists and others involved in animal experimentation; these interviews revealed a range of ideas on what systematic reviews encompass and on their applicability in animal studies. There were few known examples of relevant systematic reviews. In addition, the wording of the motion gave rise to some opposition, and some people erroneously believed that systematic reviews were to be made compulsory.

1.2 Aim: small-scale meetings to map out opportunities and challenges

- The Ministry of Economic Affairs, in charge of laboratory animal matters since 2013, wants to promote the performance of systematic reviews in animal studies, in which involvement of the profession is crucial. The Ministry of Economic Affairs invited Tabula Rasa to organize a number of small-scale meetings, aiming to get a better understanding of the added value, opportunities and challenges in animal studies, the needs of the profession, and ways in which systematic reviews can be promoted.
- Tabula Rasa organized four round table meetings. A list of participants is included in Appendix 1. All participants had ties with animal experiments, as researchers and laboratory animal experts from both universities and the industry. The meetings

involved a mix of researchers with and without experience with the systematic review methodology. In addition, a range of specialities, types of research (clinical/fundamental), universities, and young and established researchers was represented.

- The meetings were purposely restricted to the theme of systematic reviews, as a link in the chain of activities in the field and by the government aiming to improve the quality of animal studies and to accomplish the 3 Rs.
- The first three Chapters of this report are its core. Chapter 3 can be read as a summary of the results which have been elaborated in greater detail in Chapter 4. Chapter 5 presents some recommendations.

2 What is a Systematic Review?

- A systematic review is a thorough, transparent, and structured analysis of studies that have already been performed and published. This method is based on the principle that new studies should build on and add to an existing body of knowledge. A meta-analysis may but need not be part of a systematic review.
- Systematic reviews are increasingly being applied in medicine. The Cochrane Collaboration is the authority in the field of systematic reviews in medicine: their reviews are considered to be the gold standard, and their publications often have a high impact factor.
- In our round table meetings, we used the definition of systematic reviews as provided by the Dutch Cochrane Centre:

A systematic review is a structured, reproducible summary of scientific literature. Its main characteristic is the orderly, transparent, and step-wise approach to the review process:

- translating the health (care) problem into the research question;
- searching and selecting all available literature;
- critically assessing the methodological quality of the included studies;
- summarizing the results, whether or not in the form of a meta-analysis.

The final steps comprise assessing the quality of the scientific evidence, interpreting the results, and formulating the conclusion. (dccc.cochrane.org, October 2013)

3 Main Conclusions

- The main conclusions from the meetings are outlined below.

3.1 Many are unfamiliar with the methodology, particularly non-clinicians

- For a number of researchers, the Cochrane definition helped to clarify what a systematic review is: what the process involves, what its benefits are and how it differs from a traditional review or a meta-analysis. Most clinicians present were familiar with systematic reviews as they had more experience performing or using them.
- (Bio-) medical study programmes barely pay any attention to systematic reviews yet. The participants were united in their view that it is important for students and (young) researchers to learn to search systematically and to be able to assess the quality of publications in a transparent way. There is a lot to be improved in this area.

3.2 Systematic reviews have added value but should not be made compulsory

No one was opposed to systematic reviews, but there was opposition to their being made compulsory

- No one challenged the research methodology in itself. The participants agreed that it is always profitable to learn from the past and that the quality of follow-up studies may benefit from a systematic review. Amongst those who had a lot of experience with systematic reviews, there was no support for their being made compulsory, which was considered as not worthwhile and counter-effective.

Added value: systematic reviews enhance necessary quality improvement

- The performance of systematic reviews was considered to have the following added value: improved definition of research questions; improved justification for choices made (such as the animal model and the number of laboratory animals involved); the avoidance of (methodological) errors; and the opportunity to benefit from smart solutions found by other researchers. The result is a reduction in 'waste' caused by non-effective animal experiments. Opinions diverged on the question whether this would help to bring down the use of laboratory animals in the long term.

- If studies must be able to stand the rigorous test of a systematic review, participants expected that this would help to raise the overall quality of animal studies, which, as many participants indicated, leaves a lot to be desired. Many papers, for example, fail to report an experiment's blinding or randomization procedures or the control group's composition and size. Not publishing negative data (publication bias) was also considered a problem. A systematic review may expose such issues.

When are systematic reviews the most useful?

- Answers to this question ranged from 'they are always useful' to 'in my discipline, I don't think they are very useful'. Most participants felt that systematic reviews were definitely useful:
 - in large-scale new research projects involving animal experiments;
 - in retrospective studies (to assess the output of animal experiments), aiming to adapt protocols, for example;
 - prior to translation into clinical studies;
 - in common animal models;
 - in optimum methodology choice: the best transgenic method, for example.
- There was more disagreement about their added value in exploratory fundamental research and in research domains with few publications. Some researchers felt systematic reviews were important in selecting the best animal model, which was also mentioned by fundamental researchers. Others indicated that the benefits did not outweigh the effort.

Time, money, expertise, and publication opportunities as impediments

- There are some factors that may prevent researchers from choosing to do a systematic review even if this were useful:
 - Systematic reviews are time-consuming, especially if there is an abundance of available studies. Participants' experiences showed that performing a systematic review may take from one month up to more than six months.
 - Systematic reviews require a lot of expertise. Young researchers have not yet sufficiently familiarized themselves with the field, which may encumber their search for and assessment of studies. You actually need to have a team, with a content expert, a methodologist, and a librarian on board.
 - Good systematic reviews require money. Funding is rarely allocated to systematic reviews. Funding agencies expect researchers to have thoroughly examined the literature before they submit an application. Some participants performed systematic in their own time because their departments refused to invest in such reviews.
 - It is considered to be harder to get systematic reviews of animal experiments published in high-impact journals. Researchers prefer doing a new study to doing a systematic review of previous studies.

- In the industry, animal experiments must comply with set protocols. There is a lot to be gained here with systematic reviews, but this requires an international approach. The participants also mentioned access to industrial data (after a number of years, for example) as an important area deserving special attention. Such data are crucial for performing systematic reviews and for improving animal studies.

3.3 Recommendations for stimulating systematic reviews

The most important recommendations from the meetings are:

- *Integrate systematic reviews into education*
All university-based (bio-)medical curricula should include systematic reviews (systematic search strategies, transparent assessment of literature and meta-analyses). The same goes for laboratory animal science courses.
- *Offer incentives, such as specific subsidies*
Incentives are needed to stimulate systematic reviews. Some suggestions were made in the meetings:
 - Subsidies were mentioned most, a special ZonMW fund, for example.
 - Offer an award for the best systematic review, which may encourage PhD students to perform their literature search in line with this methodology.
 - Include systematic reviews as a standard component in major research programmes and make sure they are funded. Funding agencies may also require that publications should meet Arrive guidelines, for instance.
- *Improve familiarity with the methodology*
Systematic reviews of animal experiments should be part and parcel of the regular research domain. So as to be able to make an informed choice for a systematic review, researchers should be familiar with the methodology. It is important, therefore, not only to hold meetings for interested parties but also to give presentations at conferences attended by relevant researchers. It is also important to raise the number of publications and thus to raise the number of good examples. The above-mentioned incentives are also important in this respect.

4 Results of the Round Table Meetings

- This Chapter outlines the main results of the four round table meetings. It discusses the value of systematic reviews, the usefulness or uselessness of performing systematic reviews, the opportunities and challenges, and the prerequisites for stimulating this methodology.

4.1 The value of systematic reviews

- The participants felt that systematic reviews can be valuable for a number of reasons, which will be detailed in this Section.

Improving the quality of research questions

A systematic review may help to formulate better quality research questions. By closely examining other studies and assessing what has already been done and its quality, you can optimize your own research question.

Explaining variation

Some participants to the meetings observed that when many studies have been done on a particular disease or model, the results may vary. How can there be different results each time? A systematic review can help to explain variation. Certain factors often prove to have been slightly different in different experiments. A systematic review reveals what these factors are and how they may have influenced a study and, thus, clarifies what has been caused by what factors. This gives depth to a study, which is very valuable in animal studies.

*Systematic review for generating new understandings from previous studies
For the mechanism of vasodilation during pregnancy, Van Drongelen et al. (2012) performed a systematic review of the animal studies on the subject. He concluded that, in order to study the effects of mechanical and pharmacological stimuli on blood vessels during pregnancy, it is possible, feasible, and useful to perform a systematic review of animal studies. Their detailed overview of previous studies generated new understandings that would have remained undiscovered when examining isolated studies. The systematic evaluation and analysis of the animal experiments showed, for example, that stage of pregnancy has a major influence on blood vessel response. They also showed that blood vessel response is conditional upon the rat strain that was used.*

Learning from the past: avoiding pitfalls and adopting successful approaches

- ‘Systematic reviews’, as one participant put it, ‘help you to learn from the past so as to improve future research’. This may help researchers to avoid pitfalls and mistakes that have already been made by others or prevent you from ending up in a blind alley. The most successful approach coming out of the systematic review process can then be adopted in follow-up studies.

- By using quality criteria in scoring studies, a systematic review helps to make the quality of previous studies transparent in a systematic way. This helps to draft better new study designs and to prevent the occurrence of replication. Publications often fail to mention how experiments were performed (whether they were blinded and randomized, for instance). Systematic reviews make clear that there is a lot to be improved in this area.

Improving and sometimes reducing the number of animal studies by a better founded choice of animal model

- Systematic reviews may help to improve and sometimes reduce the number of animal studies by decreasing unnecessary 'waste'. For studies in which a great diversity of animal models have been used, a systematic review can demonstrate which animal model is the most effective and most feasible for translation into humans.

Systematic review for reducing the number of animal experiments

De Vries et al. (2012) showed that the number of animal experiments can be reduced in the field of cartilage tissue engineering by reducing the number of animal models used. A survey was made of the various models that had been used (ranging from rat, mouse, and rabbit to goat and horse) and their advantages and disadvantages. On the basis of this information, they concluded that reduction was indeed possible and, moreover, that choosing a particular animal model could be done in a much more evidence-based way.

Detecting publication bias

- For systematic reviews too, it is an issue that negative study outcomes are often not published, which may lead to bias in the results. Such publication bias can be demonstrated with the aid of statistics as part of a systematic review. This may reveal weak spots, though several researchers caution that, while this may give an indication of negative outcomes, it can never replace the missing data.
- It is important, therefore, that negative data should be published and be made accessible. As a positive result is more status-enhancing than a study without the desired effect, researchers might feel encouraged if scientific journals published more studies with negative outcomes. The industry should also make animal experimentation data available, after a number of years, for example. However, change is slowly but surely taking place; in 2013, for example, ZonMW launched a funding scheme for publishing negative or neutral animal experimentation data.

Systematic review demonstrates that publication bias obstructs animal to human translation

As negative or neutral results are published far less frequently than positive results (publication bias), the effectiveness of medicines may be vastly overestimated, and translation into humans may be obstructed. The same is true for animal studies that do not come up to proper quality standards.

Several research groups (Macleod, 2008; Sena, 2010; Van der Worp, 2010) examined the development of stroke treatment strategies in humans. The systematic reviews of animal studies in this field show that translation from animal studies to humans is impeded by methodological flaws in the animal experiments and the selective publication of results. Vesterinen et al. (2010) showed that this is also true for animal studies developing multiple sclerosis treatments.

Translating results to the clinic and the patient

- Improving the quality of animal experiments is very important for the translation to human studies. Clinical researchers amongst our participants said that practice shows that effects from animal experiments are certainly not always good predictors of effects in humans. There is much room for improvement here. Researchers indicated that animal experiments are often done on a gut feeling of 'what will probably work best'. By indicating what may be the best animal model, a systematic review can help to improve animal to human translation and encourage discussion of model validity.

Systematic review could have prevented mortalities in probiotics and acute pancreatitis trial

A systematic review of the use of probiotics in acute pancreatitis showed that the animal experiments led the authors to conclude that no optimal animal experiment had been conducted, causing the performance of studies in severely ill patients to be irresponsible (Hooijmans et al., 2012). The clinical trial had to be discontinued prematurely due to an unexpectedly high number of patient deaths in the probiotics group.

- This probiotics trial in people with acute pancreatitis gave rise to discussion amongst the participants. The performance of a systematic review in advance could have led to the performance of more animal trials rather than a clinical trial, which would probably have benefited patient safety. However, the question arose whether it was possible at all to design a relevant animal experiment in a case of severely ill patients. Can a sick animal be compared with a critically ill patient on the IC? In addition, as it is highly complicated to induce acute pancreatitis in laboratory animals, how can one design an animal experiment that can actually be translated to the clinic?

Systematic reviews of animal studies to generate clinical knowledge

Research by vascular surgeon Dr Warlé at the Radboudumc (Wever et al., 2012) showed that a systematic review of animal studies generates knowledge that can be directly applied in renal damage research in clinical practice. It also showed that the most commonly used protocol in the clinic is probably not the optimal one. The systematic review of renal damage studies by Wever et al. (2012) led to a new clinical trial that was based on the most effective strategy, which had been identified with the aid of the systematic review.

With the aid of a systematic review, Van der Spoel et al. (2011) showed that stem cell therapy is effective in large animal models of ischaemic heart disease. In addition, the researchers showed that the clinically relevant parameters – which influence effect size in large animals (therapy timing, for instance) – correspond to the parameters that appear to have an influence in clinical meta-analyses.

4.2 The usefulness or uselessness of performing systematic reviews

The usefulness or uselessness of performing systematic reviews depends on the type of study and its aim

- The participants disagreed on when performing a systematic review is the most useful. Some held that it is always useful to perform a systematic review: a literature study should always be done in a properly accountable and systematic manner. Others felt it depends on the type of study: if the number of studies involved is small, a systematic review will not be very fruitful. A fundamental researcher observed: 'I write a systematic review of the literature predominantly for non-experts; for them, it may reveal new facts'. There were also participants who thought systematic reviews are unnecessary as researchers know their literature. Others objected to this by observing that if you do not search and assess literature systematically, you run the risk of favouring studies that suit your purpose.

When is performing a systematic review the most useful?

- The participants to the meetings mentioned the following situations in which performing a systematic review is the most useful:
 - for common models and interventions that have been widely published;
 - to determine what animal model is the most appropriate one;
 - to choose the optimum methodology, the best transgenic method, for example;
 - for retrospective studies that aim to assess what animal studies have yielded before they are translated to the clinic;
 - for novel research programmes when you do not yet have any knowledge of the literature and want to establish a clear starting-point;
 - for major research programmes (such as 3-4 year PhD programmes) that involve sufficient funding and brainpower;
 - when there is a lot of variation in the outcomes of studies and, hence, insecurity about the effects.

When is a systematic review less useful?

- Some participants felt that it is not always self-evident to perform a systematic review: it is not always possible to do meta-analyses, for example when studies are too heterogeneous. However, participants with expert experience indicated that performing a systematic review can be useful for follow-up studies in this case too.

Particularly in the case of fundamental research of an exploratory kind, the majority of participants was not convinced of there being any added value, though some thought there was: here too you need to select an animal model, and some fundamental researchers make use of systematic reviews to do so.

- Then there are practical reasons why a systematic review may not seem useful, as in the case of a minor short-term research project, or when the time-investment outweighs its expected returns.

The usefulness of systematic reviews when there are few publications

- Some researchers observed that they cannot do a systematic review if there are few data. Others felt this was an advantage: when there are no meta-analyses to be performed, the process takes little time, and the outcome is that you know what literature is available and that your search has been systematic and transparent. For researchers, it is precisely this outcome – that there are only few publications – that can be interesting: it shows what knowledge gaps there are and, hence, points out new research opportunities.

Systematic review shows up knowledge gaps (when there are few publications)

In collaboration with Syrcle, drs. Reus (Prader-Willi Foundation) (Reus et al. 2012) performed a systematic review of animal studies of the Prader-Willi Syndrome. Animal model studies could improve our understanding of neuromuscular deviations in children with this syndrome. A total of 401 studies were screened, 9 of which were included. Out of these 9, only 2 dealt with neuromuscular deviations, too small a number for performing a meta-analysis.

Despite the low number of included studies, the systematic review of neuromuscular deviations in children with the Prader-Willi Syndrome did produce results, according to the researchers involved:

- *the researchers now knew exactly what the value of their study was from a scientific point of view;*
 - *the review pointed at new research opportunities;*
 - *it made clear that new animal models probably needed to be developed to be able to examine or answer the research question (possible muscular deviations causing hypotonia) in the future, as most models focus on just one aspect of the disease: possible deviations in motor control.*
- Some fundamental researchers did not think the outcomes of such an exercise were worth it. Considering the time it takes to retrieve relevant articles from the search and to comprehend the methods (which are much more complex in preclinical than in clinical trials), they did not think that the few additional articles would pay off. They preferred to have the information that could quickly be obtained in a regular review. They did think, however, that a systematic review was

valuable for identifying the most appropriate animal model. One participant wondered what would happen if the one extra article you got out of your systematic review, which you would have missed otherwise, was the one you were planning to do your experiment about? If you excluded this article from your literature review, this would lead to unnecessary duplication and waste.

4.3 Opportunities and challenges in practice

- The opportunities and challenges presented by systematic reviews tend to be interlinked; therefore, we will deal with them together in this Section.

Uncertainty about what a systematic review is

- The meetings showed that there was some uncertainty about what exactly a systematic review is. We observed there were two common misconceptions:
 - a systematic review is the same as a thorough literature study;
 - a systematic review is the performance of a meta-analysis.
- Experts explained that a systematic review is distinguished by the following three features:
 - searching procedures in systematic reviews are more structured and systematic, making the literature study reproducible;
 - the quality of the articles is scored by means of pre-defined criteria in a systematic and transparent way;
 - a meta-analysis can be but need not be part of a systematic review.

Systematic reviews and systematic searches: not embedded in research and education

- At present, little or no attention is paid to systematic reviews in (bio-)medical study programmes, causing researchers to be unfamiliar with the methodology or unaware of how to perform systematic reviews and when it is useful to do so.
- The expertise required for embedding systematic reviews in education and research is not available at all universities. Participants pointed out that this knowledge is available at the Dutch Cochrane Centre and at Syrcle, amongst others.
- A systematic literature review goes beyond a PubMed search using keywords. It requires another way of searching in different databases and in different languages. By searching systematically, you obtain a complete picture of the literature. Participants with systematic reviewing experience said they believe that searches are rarely truly systematic. Barring exceptions, study programmes pay insufficient attention to systematic searches, and students are generally unable to do them properly after graduation. It is, however, an essential element in research.

Systematic reviews: a team effort - insufficient expertise available

- Most participants agreed that a systematic review should always be a team effort. Various domains of expertise are involved, and it is important for team members to be able to confer on the approach and the research question. The process requires, at least, knowledge of methodology, statistics, the content domain, and a librarian's searching expertise.
- A meta-analysis was considered by some researchers as involving the highest possible burden of proof. Some, therefore, cautioned that its use in animal studies demands careful consideration: what data can and what data cannot be taken together? What conclusions can be drawn from a meta-analysis? Experts said that the systematic review system takes all this into account.
- At present, researchers are largely unfamiliar with systematic reviewing proceedings. A systematic review or meta-analysis should not be lightly undertaken, as they require specific expertise. Syrcle has this knowledge and has meanwhile gained a lot of experience, sharing its expertise in workshops and supporting systematic reviews at various universities. This expertise should not remain restricted to Syrcle but should be made available to all universities.

Funding for systematic reviews hard to obtain in research applications

- It is difficult at present to obtain funding for systematic reviews. Opportunities for submitting funding applications for systematic reviews in themselves are few and far between. It is even harder to get a systematic review incorporated into a bigger research funding application: funding agencies like to have a well-founded understanding of the project that is to be funded, and a systematic review suggests that the researcher does not yet have a firm grasp of the current state of affairs. In addition, the outcome of a systematic review may imply changes being made to the research design (such as the choice of animal model), which may affect the required funding. This involves too many uncertainties for funding agencies, which, in its turn, presents a dilemma for researchers.

Major time investment required

- Performing a systematic review requires a lot of time. One of the participants to the meetings wondered how this time demand is to be met. One researcher, convinced of its importance, spent evenings and weekends working on systematic reviews as the department was unable or unwilling to invest. Participants wondering how changes can be made, had the following questions:
 - What must be done by researchers and what can be done by others? Perhaps a librarian can be involved to do the literature search.
 - Is it possible to do a quickscan?
 - When do the results need to be brought up to date?
- Researchers observed that performing a systematic review is a tedious process: the process may take up to half a year.

The quality of animal studies and reporting methods needs to be improved

- Virtually all participants said that the methodological quality of animal studies requires major improvement, as many studies still show fundamental errors, with blinding and randomization often left undone or unreported. The participants disagreed on whether, when blinding and randomization go unreported, this means that these procedures have not been done. Systematic review experts said that when they contacted authors of such articles, blinding and randomization hardly ever proved to have been performed. The necessity of improved reporting standards is recognized by everyone. Current reporting standards compromise systematic review quality: rubbish in is rubbish out.
- It is important for a systematic review that data of previous studies should be retrievable and available, which ties in with the availability of literature in databases and the publication and release of (negative) research data. The data you use, should be reliable. If the quality of studies to be included in a systematic review is poor, this affects the usefulness of the outcomes. This is why, as more and more systematic reviews are to be implemented, the quality of studies needs to go up at the same time.
- Some participants with systematic review experience said that, in practice, when a clinical trial has failed, the literature is sometimes thoroughly examined in retrospect. Researchers may then opt to perform a systematic review to establish the total output of animal experiments. This sequence had better be reversed to prevent the performance of unnecessary clinical trials.

The industry: a lot to be gained

- The industry tends to operate with prevailing international protocols, which, the researchers said, are not well-founded. This implies that, though animal experiments are performed in the same way, the chosen research design may not be the most effective one. There is a lot to be gained with systematic reviews. Both the regulators and the industry itself might take the lead here.
- The industry possesses a wealth of unpublished research data, which it refuses to release. It would be very valuable if such data were to be made available after a number of years for use in meta-analyses, for instance.
- The threshold for performing systematic reviews appears to be higher in the industry and in commercial research institutes than in science. The industry's core business is to develop new medicines, and it is under pressure to introduce new products fast. Systematic reviews take time, and time is at a premium. Some participants working in the industry said that the predictive value of animal studies is small, and that systematic reviews may help to improve the relevance of animal studies in animal-to-human translation processes.
- Companies working in the food industry prefer human studies to animal studies. Food tests are increasingly done in humans as they are relatively easy to carry out

in humans, which greatly improves the relevance of results. The food industry prefers not to be associated with animal experiments as animal research remains a sensitive issue.

Improving international competitive edge with innovative research

- In one of the meetings, participants suggested the Netherlands might profile itself with systematic reviews of animal experiments at the international level: an innovative approach to animal experiments may reinforce our competitiveness.
- We should be sharing the systematic review system and methodology on a wider national and international scale rather than keeping our cards close to our chest.
- Cochrane can help to attain such a position in animal studies at the international level. With the support of the Ministry of Economic Affairs, we can access European channels, which is presently unfeasible due to lack of funds, according to participants. 'This is a European theme where we want to keep our competitive edge and build an international profile.'

Constraint: low status and opposition from fellow researchers

- Performing systematic reviews carries a number of risks, one of which is that established researchers are not keen to have their projects and publications closely examined or to have quality issues pointed out to them. This may give rise to opposition and cause established researchers to be reluctant to collaborate or participate in systematic reviews.
- In the field of science, systematic reviews in the animal experimentation domain are low status: they are looked down upon as unoriginal and as drawing on other people's work. This is not the case in the field of medicine, where your clinical trial counts as being high quality when it is included in a systematic review and where a systematic review helps you to get high ratings on the citation index. In animal studies, it is difficult to get systematic review results published, though things are gradually changing.

4.4 Stimulating systematic reviews

Stimulating systematic reviews rather than making them compulsory

- Before the start of the meeting, the participants were informed that systematic reviews were not to be made compulsory. Most participants already knew this, but some did not. Particularly those who had done a Google search on the motion in the Lower House to prepare for the meeting were still a little confused. Some fundamental researchers felt its wording ('*systematic reviews to become the norm in animal studies like in regular science*') was unnecessarily offensive and incorrect, as if they did not perform regular science.
- The participants believed there was no point in making systematic reviews compulsory. This would only serve to foster opposition and increase the likelihood

of people rushing through a review or committing fraud, none of which would be helpful.

- Some participants were in favour of taking more charge, by setting requirements on research funding and publications, for example. Funding agencies and journals can exert an influence: if they set requirements, people are more inclined to meet them. This may help to initiate change and make the performance of systematic reviews more common in animal experiments. Others preferred to see the introduction of positive stimulating measures.

Financial support

- In the course of the meetings, it became clear that financial incentives (including government incentive schemes) would be imperative to boost the implementation of systematic reviews. The following suggestions were made:
 - ZonMW grants;
 - to ask health funds for targeted systematic reviews;
 - to apply to a KNAW fund where systematic review applications are eligible for submission;
 - to launch a competition for systematic reviews of animal experiments, with a prize that is relevant to young researchers;
 - to open up the 'Alternatives to Animal Experiments' fund to systematic reviews;
 - to explore the opportunities offered by Horizon 2020.

Content support: utilize and share available expertise

- In addition to financial support, specific expertise is essential. Syrcle has this expertise and should be given a greater role in its dissemination.
- Animal labs currently lack sufficient capacity and expertise to be able to perform systematic reviews. Reinforcement is required and may help to promote the implementation of systematic reviews.

Implementation in education

- Participants to the meetings felt it was vital for the systematic review methodology and systematic searches to be embedded in the education system. At present, students are insufficiently trained to perform systematic searches and are insufficiently familiar with the methodology. Educational programmes pay little or no attention to systematic reviews. All participants agreed it was important for students to improve their literature searching skills. This is often a missing skill in post-graduates.
- Too little expertise is currently available to include systematic review courses into study programmes. There are, however, some strong research groups that might pioneer such a development. Some suggested that systematic reviews should be included in medical and biomedical Master's programmes. Embedding in FELASA category C (Article 9) courses is also important. The participants felt that post-

graduate academics should be able to perform a systematic review: *'It isn't rocket science'*. Such embedding can be guaranteed by including systematic reviews as an attainment target in studies involving animal research.

Embedding systematic reviews in research proposals

- Some participants suggested that the literature section in applications for animal studies should meet the requirements for a systematic review and that, if appropriate, a meta-analysis should be part of the research proposal. This means that reviewers of research proposals should also be sufficiently familiar with the methodology to be able to accommodate this in their assessment.

Journals: observing Arrive guidelines

- The participants pointed out that the Arrive guidelines now used by several high-impact journals are a major step forward, even if it will take some time before all reviewers will be able to apply them in their assessments. Reviewers should be facilitated and encouraged to make sure authors adhere to these guidelines.
- Research institutions should make sure that articles meet the Arrive guidelines as a standard, which is already common practice at some institutions. One of the participants reported afterwards that a recent analysis of the impact of Arrive guidelines showed that no progress has been made in the last two years.

DECs (ethical review committees) to play central role in monitoring animal experiments

- By registering animal experiments in a central register (through DECs, for instance) and monitoring the outcomes, even if they are negative, you get a better idea of negative data, which can be used in systematic reviews. It is also highly recommended to gain a better understanding why, for instance, only eighteen mice were left at the end of an experiment when there were twenty at the start. It is highly relevant for animal to human translation to know the cause of these deaths.

Communicating best practices on wide scale

- Communicating successful systematic reviews on a wide scale may help to impress upon researchers the added value and the benefits of performing systematic reviews. If such successes were only disseminated amongst those who are already familiar with the methodology, we would be preaching to the converted.

5 Policy Recommendations

- On the basis of the round table meetings and talks with experts involved, we have drafted the following recommendations for the Ministry of Economic Affairs with a view to accelerating the implementation of systematic reviews.

5.1 Embedding systematic reviews in education

Embedding systematic reviews in medical and biomedical Master's and postdoc programmes

- To make sure that systematic reviews are properly embedded in animal studies, general familiarity with the methodology needs to be improved, starting with Master's courses. At present, medical and biomedical study programmes largely ignore systematic reviews as a methodology for performing replicable literature studies and meta-analyses. Unfamiliarity means non-application.
- For the quality of animal studies, it is essential for systematic reviews to be included in the curriculum and for students, particularly research Master's students, to gain experience with them. We recommend that this should be stimulated in the following ways:
 - by contacting the methodology sections and the Directors of Education of medical and biomedical study programmes, which could be done on a personal basis or in an exploratory study;
 - by inviting the VSNU (Dutch organisation of universities) and the NFU (Dutch organisation of university medical centers) to support systematic reviews in Master's and young researcher programmes;
 - by offering widely available educational materials to be used in study programmes, possibly after these have been adapted to local educational circumstances (see also 5.2).

Inclusion in laboratory animal science courses

In passing the *Wet op de Dierproeven* (Animal Experimentation Act), it was noted that animal science courses should pay attention to systematic reviews, without specifying how this was to be done. It is a matter of some urgency to define the knowledge and competencies that students taking laboratory animal science courses can be expected to have.

- We advise the Ministry to invite those in charge of laboratory animal science courses to draft a content and implementation proposal.

5.2 Course development

Further education and career training courses focusing on performing systematic reviews

- The proper performance of systematic reviews requires specific expertise. This goes for both literature studies and meta-analyses.
 - We recommend the development of further education and career training courses for researchers, to be funded for a number of years. Besides the one-day workshops offered by ZonMW, there is also a need for more elaborate training and coaching during the implementation of systematic reviews.

The development of education modules

- Systematic review expertise is not available across the board. To accelerate the process, it would be advisable to make sure that a high-quality module is on offer.
 - We advise the development of a basic e-learning module that is suitable for both students and researchers or for DEC (ethical review committee) members, for instance, who wish to improve their proficiency in this methodology. With a view to the study programmes' international character, it would be evident to use English as the medium of communication.

5.3 Stimulating the performance of systematic reviews

Setting up a funding scheme

- Systematic reviews are more established in human research than in animal research, and hence it is difficult to obtain funding for systematic reviews of animal studies. A funding scheme will help to remove this impediment and to raise the performance of systematic reviews.
 - We recommend the establishment of a funding scheme, through ZonMW, for example. This could be a temporary measure to increase the number of good examples.
 - In new, government-funded research programmes that involve animal experiments, the Ministry could use its network to promote systematic reviews being included in the programme.

Performing systematic reviews for common animal models

- The meetings made clear that there are subject areas in which many researchers would benefit from systematic reviews.
 - We advise the Ministry to identify the most eligible subject areas and to commission the performance of a systematic review as a research assignment.

Award

- A best systematic review award may work as an incentive. It might target researchers working on a PhD thesis, for example, and stimulate them to perform their literature study in conformity with systematic review requirements.

Lectures and workshops at regular medical and biomedical conferences

- Researchers themselves can also make a contribution by delivering lectures on the results of systematic reviews at regular medical and biomedical conferences. Meetings such as symposiums and congresses on systematic reviews or the 3Rs are generally attended by a selective audience and fail to reach out to animal researchers with other preoccupations. You are just addressing the fan base.
 - This particularly requires making use of personal networks, to which the Ministry could also make a contribution.

References

- Cochrane (2013), *Dutch Cochrane Centre – Veelgestelde vragen*. Beschikbaar op het World Wide Web: <http://dcc.cochrane.org/nl/veelgestelde-vragen#2> wat is SR. Geraadpleegd op 19 december 2013.
- De Vries RBM, Buma P, Leenaars M, Ritskes-Hoitinga M, Gordijn M. (2012), *Reducing the number of laboratory animals used in tissue engineering research by restricting the variety of animal models. Articular cartilage tissue engineering as a case study*. [Tissue Engineering](#) Part B: Reviews 18(6): 427-35.
- Hooijmans CR, de Vries RBM, Rovers MM, Gooszen HG, Ritskes-Hoitinga M. (2012), *The Effects of Probiotic Supplementation on Experimental Acute Pancreatitis: A Systematic Review and Meta-Analysis*. [PLoS One](#). 2012;7(11):e48811
- Macleod MR, van der Worp HB, Sena ES, Howells DW, Dirnagl U and Donnan GA. (2008), *Evidence for the efficacy of NXY-059 in experimental focal cerebral ischaemia is confounded by study quality*. [Stroke](#) 39: 2824-29
- NKCA - Nationaal Kenniscentrum Alternatieven voor dierproeven (2013), *Systematic reviews*. Beschikbaar op het World Wide Web: <http://www.nkca.nl/3v-alternatieven/vervanging-vermindering-verfijning/vermindering/systematic-reviews/>. Geraadpleegd op 23 december 2013.
- Reus L, Hooijmans CR, van Alfen-van der Velden J, Ritskes-Hoitinga M, Nijhuis-van der Sanden R. (2012), [Mini Symposium](#) Systematic review animal studies – *Can animal studies provide insight into neuromuscular functioning in Prader Willi syndrome?* Radboud Universitair Medisch Centrum Nijmegen.
- Sena ES, van der Worp HB, Bath PM, Howells DW, Macleod MR. (2010), *Publication bias in reports of animal stroke studies leads to major overstatement of efficacy*. [PLoS Biol](#). 8(3):e1000344.
- Van der Spoel TIG, Jansen of Lorkeers SJ, Agostoni P, van Belle E, Gyöngyösi M, Sluiter JPG, Cramer MJ, Doevendans PA, Chamuleau SAJ. (2011), *Human relevance of preclinical studies in stem cell therapy: Systematic review and meta-analysis of large animal models of ischaemic heart disease*. [Cardiovasc Res](#) 91: 649–658.
- Van der Worp HB, Howells DW, Sena ES, Porritt MJ, Rewell S, O'Collins V, Macleod MR. (2010), *Can animal models of disease reliably inform human studies?* [PLoS Med](#). 7(3):e1000245
- Van Drongelen J, Hooijmans CR, Lotgering FK, Smits P, Spaanderman ME. (2012), *Adaptive changes of mesenteric arteries in pregnancy: a meta-analysis*. *Am J Physiol Heart Circ* [Physiol](#) 303, H639-H657

Vesterinen HM, Sena ES, French-Constant C, Williams A, Chandran S, Macleod MR. (2010), *Improving the translational hit of experimental treatments in multiple sclerosis*. [Mult Scler](#). 16(9): 1044-55.

Wever KE, Menting TP, Rovers M, van der Vliet JA, Rongen GA, Masereeuw R, Ritskes-Hoitinga M, Hooijmans CR, Warlé MC. (2012), *Ischemic preconditioning in the animal kidney, a systematic review and meta-analysis*. [PLoS One](#), 7(2), e32296. [Epub 2012 Feb 28]

Appendix I – Participants Round Table Meetings

- The following persons attended and participated in the four round table meetings (in alphabetical order):
 - Ms B. (Brenda) Bakker - PhD student at University of Twente
 - Prof. dr. J.G.G. (Gerard) Borst – Full Professor Neurophysiology, Vice-chair of The Department of Neuroscience at Erasmus Medical Center Rotterdam
 - Dr. T. (Tessa) Buckle - Postdoc Radiology at Leiden University Medical Center
 - J. (Joris) van Drongelen, MD – Gynaecologist at Radboud University Medical Center
 - Prof. dr. Y. (Ype) Elgersma – Full Professor Molecular Neuroscience at Erasmus Medical Center in Rotterdam. Scientific Director of ENCORE (Expertise Centre for Neurodevelopmental Disorders)
 - Dr. J.M. (Martje) Fentener van Vlissingen - Director of Erasmus MC Laboratory Animal Science Center, Chair of the Dutch Association for Laboratory Animal Science
 - Prof. dr. R.A.M. (Ron) Fouchier - Endowed Professor of Molecular Virology at Erasmus Medical Center Rotterdam. Member of the council for Medical Sciences (RMW) of the KNAW (Royal Academy Institutes), member of the Central Committee on Animal Experimentation (CCD), chairman of the medical and veterinary subcommittee of the Committee Genetic Modification (COGEM)
 - Prof. dr. H. (Harry) van Goor – Full Professor, Department of Surgery, Radboud University Medical Center Nijmegen
 - Prof. dr. J.L.M. (Joost) Gribnau – Endowed Professor of Epigenetics at the Department of Reproduction and Development at Erasmus Medical Center Rotterdam.
 - Dr. H.A. (Henriette) Griffioen – Medical biologist and animal welfare officer at Academic Medical Center Amsterdam
 - Dr. L. (Lucianne) Groenink – Associate Professor of Psychopharmacology at the Faculty of Science, Utrecht University
 - Prof. dr. C.F.M. (Coenraad) Hendriksen – Full Professor Alternatives to animal testing at the Department of Animals in Science and Society of the Faculty of Veterinary Medicine - 3R Centre Utrecht Life Sciences
 - Dr. C.R. (Carlijn) Hooijmans – Researcher at Syrcle (Systematic Review Centre for Laboratory animal Experimentation)
 - Drs. S.J. (Sanne) Jansen of Lorkeers - PhD student in Cardiology at the University Medical Center Utrecht, member of CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies)
 - Prof. dr. ir. A.H. (Sander) Kersten – Full Professor in Molecular Nutrition at Wageningen University
 - Dr. C.A.M. (Cyrille) Krul - Business line manager in Biomedical Innovations at TNO; Professor Alternatives to Animal Testing at the University of Applied Sciences Utrecht

- Dr. C. (Cindy) Kunne – Researcher at Academic Medical Center Amsterdam
- Dr. Ir. M. (Marlies) Leenaars – Assistant professor at Radboud University Medical Center Nijmegen, researcher at Syrcle (Systematic Review Centre for Laboratory animal Experimentation)
- Dr. P.J.K. (Peter) van Meer – Postdoctoral researcher in biopharmaceutics at Utrecht University
- Prof. dr. T.W. (Theo) Mulder - Director Research at the Royal Academy Institutes in the Netherlands
- Dr. G. (Gerben) ter Riet – Epidemiologist at Academic Medical Center Amsterdam.
- Prof. dr. M. (Merel) Ritskes-Hoitinga - Professor in Laboratory Animal Science at Radboud University Medical Center Nijmegen
- Prof. dr. H. (Huub) Schellekens, MD, PhD – Full Professor of Pharmaceutical Biotechnology, Departments of Pharmaceutical Sciences and Innovation Studies, Utrecht University
- Prof. dr. R.J.P.M. (Rob) Scholten- Director of the Dutch Cochrane Centre, Full Professor of Clinical Epidemiology with a focus on evidence-based medicine at the University of Amsterdam’s Faculty of Medicine
- Prof. dr. M.E. A. (Marc) Spaanderman – Full Professor Transmural Obstetrics at the Department of Health, Medicine and Life Sciences at Maastricht University
- Dr. F.R. (Frans) Stafleu - Assistant Professor Humanities, Department of Philosophy and Religious Studies at Utrecht University
- Dr. A.A. (Anje) te Velde – Researcher at Academic Medical Center Amsterdam
- Dr. Ir. I. (Irma) Vijn - Senior Policy Advisor at HollandBIO
- Dr. M.C. (Michiel) Warlé – Vascular surgeon at Radboud University Medical Center Nijmegen
- Dr. J.G. (Jan) Wolters – Animal science specialist at Academic Medical Center Amsterdam
- Dr. H.B. (Bart) van der Worp – Clinical Neurologist, Department of Neurology at University Medical Center Utrecht, member of CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies)