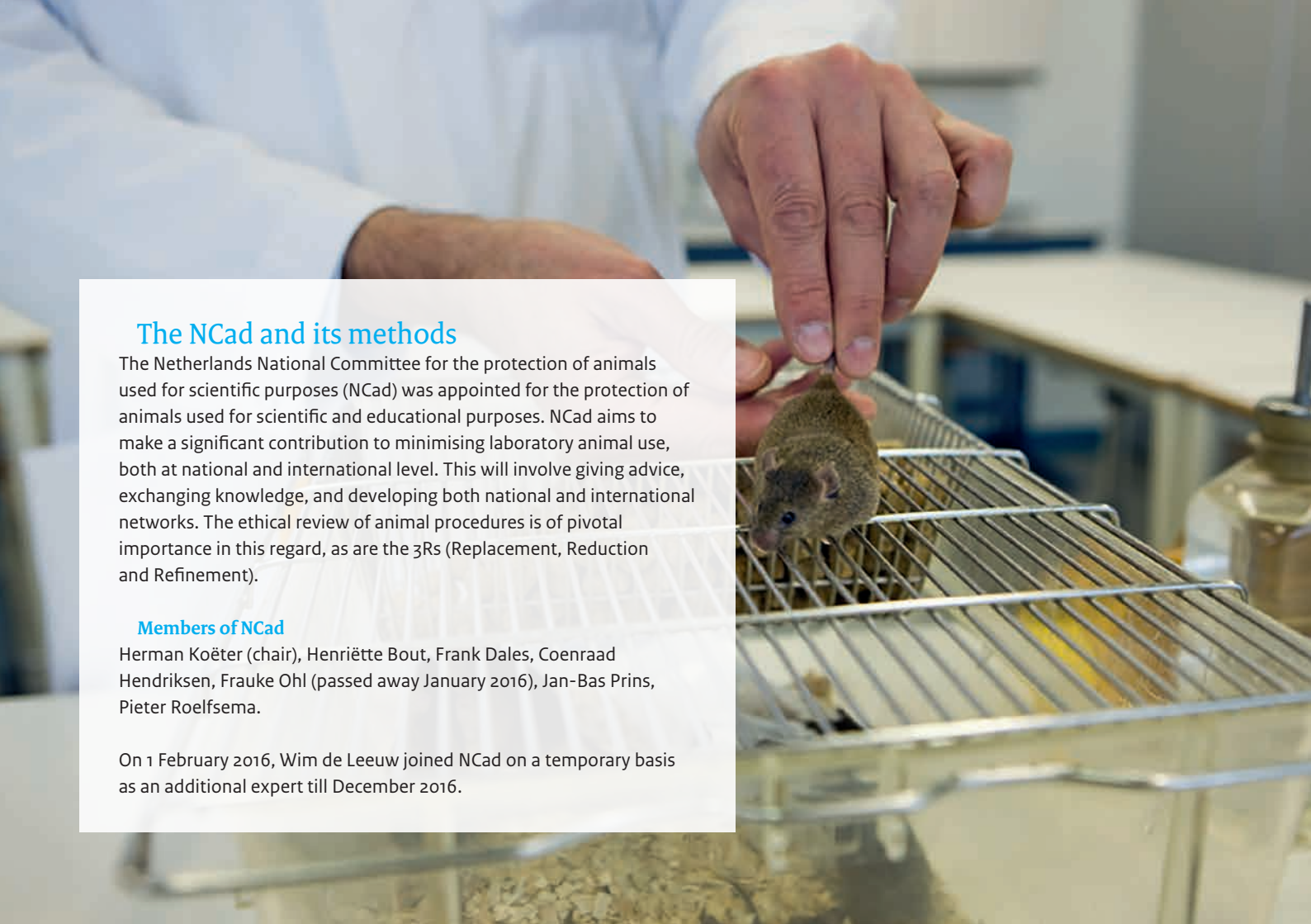
Netherlands National Committee
for the protection of animals
used for scientific purposes

Synthesis of Evidence in laboratory animal research

Opinion of the Netherlands National Committee for the protection of animals used for scientific purposes (NCad)



The NCad and its methods

The Netherlands National Committee for the protection of animals used for scientific purposes (NCad) was appointed for the protection of animals used for scientific and educational purposes. NCad aims to make a significant contribution to minimising laboratory animal use, both at national and international level. This will involve giving advice, exchanging knowledge, and developing both national and international networks. The ethical review of animal procedures is of pivotal importance in this regard, as are the 3Rs (Replacement, Reduction and Refinement).

Members of NCad

Herman Koëter (chair), Henriëtte Bout, Frank Dales, Coenraad Hendriksen, Frauke Ohl (passed away January 2016), Jan-Bas Prins, Pieter Roelfsema.

On 1 February 2016, Wim de Leeuw joined NCad on a temporary basis as an additional expert till December 2016.

Summary

In this position statement, NCad describes the use of various Synthesis of Evidence (SoE) methods in planning and conducting laboratory animal research and the contribution of these methods to 3Rs policy. Careful preparation for laboratory animal research is evidently important and necessary for its quality and acceptance in society.

Media attention has possibly created the impression that a large percentage of animal procedures could have been avoided if an SoE method, such as Systematic Reviews (SRs), would be applied more generally. According to NCad, SoE makes a crucial contribution to the quality of laboratory animal research, yet the NCad also points out that SoE can sometimes lead to an increase in the number of laboratory animals in an experiment because this improves the study design in certain situations. An analysis of many animal procedure publications does reveal, however, that there is often a lack of essential information relating to the experimental design.

SoE is an umbrella term for the various forms of classifying and evaluating available scientific knowledge as substantiation for a proposed animal or other procedure. Narrative reviews (descriptive literature reviews) are the most flexible form and systematic reviews (SRs) are the most complete and time-intensive.

In addition, open-access databases can be consulted with regard to the choice of animal models or 3R alternatives. Expert panels can also be used to discuss a specific scientific question.

NCad regards SoE in all its facets essential to enhance the quality of research questions and the design of laboratory animal research. The exact chosen SoE form depends on the specific research question and available knowledge. Limitations to the application of SoE are that essential information regarding the design of the procedure often lack from publications, negative results are seldom published and the results of animal procedures can not be disclosed due to professional confidentiality.

To encourage the application of SoE, NCad makes a number of recommendations to the field of biomedical research:

1. Encourage the application of a documented SoE in the design of a research project that considers the use of laboratory animals, but bear in mind that the scope and depth of the SoE depends on the available knowledge regarding the research question and the field.

2. When providing grants, the providers of those grants should promote the full spectrum of SoE, in particular also the creation and updating of relevant databases regarding the applicability of animal models.

3. Assessors of projects involving animal procedures, such as the Animal Ethics Committees (DECs), the Central Authority for Scientific Procedures on Animals (CCD), and Animal Welfare Bodies (IvDs) are advised to critically assess the application of SoEs during the assessment of projects.

4. Encourage attention and appreciation amongst researchers for the importance of publishing negative results and replications of earlier studies by, for example, incorporating this subject more firmly in training courses and in the criteria by which scientists are assessed.

NCad will seek to have an ad hoc expert working group appointed at European level, comprising members from the Netherlands and other Member States, to draw up a harmonised code of practice for applying the SoE concept to the process of choosing between an animal procedure, an alternative procedure or abandoning an experiment.

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1. Introduction

Over the last few years, much of the attention in the societal debate on scientific research with laboratory animals has focused questioning on whether laboratory animal research is always necessary and correctly designed. It is imperative to focus on the meticulous preparation of scientific research plans and to make optimal use of existing knowledge. By means of this position statement, NCad hopes to contribute towards the careful application of Synthesis of Evidence (SoE). NCad also wishes to provide clarity on the use of SoE methods in planning and conducting laboratory animal research and show how these methods contribute towards the 3R policy.

1.1 What is synthesis of evidence (SoE)?

SoE is the synthesis of relevant literature and expertise in order to arrive at scientific, well-substantiated and accessible summaries of the information that is available before research commences. This is essential for substantiating the choice of the most relevant research model. It also assist in preventing unnecessary duplication of research and in choosing the correct experimental design, particularly but not only in relation to animal models.

SoE is an umbrella term. There are different ways to classify the available scientific knowledge, namely:

- Narrative reviews (descriptive literature research). This is the most flexible form of review and is used in all fields of study.
  The disadvantage is that the selection of studies used for the evaluation is often arbitrary because an exhaustive literature search is not always carried out and selective references to publications can be made. Narrative reviews can be limited (such as in an exploratory study in a practically untouched area of research) or comprehensive (such as a monograph).
- Systematic review (SR). This type of review involves as complete a literature search as possible into the research topic and selection of the studies for inclusion in a systematic and exhaustive manner. SR is particularly suitable for specific research questions and has specific added value for topics for which many publications are available. The method mainly uses meta-analytical and other statistic processes and is labour intensive.
- Databases contain information on animal models and other information that is relevant to the research. These can be consulted during preparation both for laboratory animal research and for narrative and systematic reviews.
- Expert panels are groups of experts that come together to discuss a specific scientific question and issue a report in that regard, such as the possibilities and limitations of the 3Rs in a particular field of research.

Figure 1. Synthesis of evidence is an umbrella term. Performing a systematic review is more complex and takes more time than a narrative review.

2. Conclusions

Careful preparation for laboratory animal research is evidently important and necessary for its quality and acceptance in society. NCad groups many different methods under the heading of SoE, which, depending on the research question, can and must be used for that purpose.

In NCad's opinion, discussions over the last few years have focused too much on SRs, one of the SoE methods. This has created the impression that a large percentage of animal procedures could have been prevented if SRs had been applied in all cases. NCad believes that SoE is essential to the quality of laboratory animal research, yet points out that SoE can also lead to an increase in the number of laboratory animals in an experiment if that improves the study design. Analysis of many animal procedure publications does reveal, however, that there is often a lack of essential information relating to the experimental design. NCad regards SoE in all its facets as an important means to increase the quality of research questions and the design of laboratory animal research.

Narrative reviews can be applied to almost all research domains and can provide a compact yet informative account of current scientific understanding. SR can play an important role in the phase before a clinical study is chosen, particularly if many studies have already been carried out (Swankhuisen & Smit, 2014). Designated databases and SRs can be valuable aids in the search for the correct animal model for a disease. Carefully constituted expert panels are also useful to address questions regarding the applicability of animal models and the implementation of the 3Rs. European and national authorities frequently make use of such expert panels.

SoE is an integral part of the current scientific practice because research applications and scientific studies nearly always start with a description of current scientific understanding. The manner in which researchers report on laboratory animal research, which regularly reveals gaps and often does not describe negative results, is an obstacle (Macleod et al., 2015). Although these shortcomings in reports complicate the performance of SoE, this does not alter the fact that SoE is essential for the quality of research.

Too little information is available to be able to assess the extent to which further promotion of the structural and documented performance of SoE could reduce the number of laboratory animals used, improve scientific information and/or enhance the translation of laboratory animal results to human medicine (Hooijmans & Ritskes-Hoitinga, 2013). NCad argues nonetheless for more carefully substantiated use of laboratory animals and therefore recommends that researchers abide by a code of practice for the reasoned justification of every procedure design. However, NCad sees no direct relationship between such code and laboratory animal usage. NCad also has no indications that SoE is inadequately covered during the education of researchers.

2.1 NCad recommendations

NCad makes the following recommendations to the biomedical research field:

1. Encourage the application of a documented SoE in the design of a research project that considers the use of laboratory animals, but bear in mind that the scope and depth of the SoE depends on the available knowledge regarding the research question and the field.

2. When offering grants, the providers of those grants should promote the full spectrum of SoE, in particular also the creation and updating of relevant databases regarding the applicability of animal models.

3. Assessors of projects involving animal procedures, such as the Animal Ethics Committees (DECs), the Central Authority for Scientific Procedures on Animals (CCD), and Animal Welfare Bodies (IvDs) are advised to critically assess the application of SoEs during the assessment of projects.

4. Encourage attention and appreciation amongst researchers for the importance of publishing negative results and replications of earlier studies by, for example, incorporating this subject more firmly in training courses and in the criteria by which scientists are assessed. (Macleod et al. 2014)

NCad will seek to have an ad hoc expert working group appointed at European level, comprising members from the Netherlands and other Member States, to draw up a harmonised code of practice for applying the SoE concept to the process of choosing betweenan animal procedure, an alternative procedure, or abandoning an experiment.

3. Reasoning

3.1 Introduction

During the process of writing research proposals and project applications, researchers perform an SoE, so ethical aspects can be taken into consideration in the choices made with respect to the research design. After the Animal Ethics Committees and Animal Welfare Bodies have rendered their opinion on the research proposal, the Central Authority for Scientific Procedures on Animals (CCD) carries out ethical testing, in which the degree of discomfort for the laboratory animal concerned is an important factor, prior to deciding on the project proposal.

The Montreal Declaration, accepted in 2011 by the Eighth World Congress on Alternatives and Animal Use in the Life Sciences, expressed this as follows:

Performing an SoE marks the start of the process of making a research proposal and aims to clarify what knowledge is and is not already available in order to enhance the quality of further research (Grimshaw, 2010). SoE can prevent the unnecessary repetition of laboratory animal studies that have already been conducted and contribute towards the transparency of translating the results of laboratory animal research and the proper design of clinical studies in human medicine. In this way, the SoE significantly contributes towards the implementation of the 3Rs.

The past few years has received a lot of attention in the Dutch parliament and among researchers in SoE, and particularly SR, as a

means to improve the quality of laboratory animal research and limit the use of laboratory animals in research. In 2012, the House of Representatives accepted a motion to make SRs the norm in laboratory animal research. However, it frequently happens that there are an insufficient number of relevant studies to perform an SR and one of the other forms of SoE is usually applied in these cases.

It is important to emphasise that knowledge acquired through an SR or other form of SoE can also result in the need for subsequent studies to be carried out in larger groups of animals because smaller groups produced information that was not sufficiently reliable from a statistical perspective (Egan & Macleod, 2014). In this case, the contribution of SoE is that studies with small groups are avoided, but the example also illustrates that it is uncertain whether the application of SoE will reduce the total number of laboratory animals used on a larger scale (De Vries et al., 2014).

3.2 SoE: exploratory literature search to justify the choice of whether or not to carry out an animal procedure

A choice can be made from a number of forms of SoE when synthesising information from the relevant literature and other available material.

3.2.1 Narrative review

This form of review is used to catalogue developments in a scientific domain. Narrative review is widespread and used in practically every area of science. One disadvantage of this method is that the manner in which studies are selected is often not documented and therefore cannot be reproduced by others.

A major advantage is the flexibility of this method, allowing for current scientific understanding in each domain to be described, even if only little information is available on the topic.

3.2.2 Systematic review (SR)

SR is an extension of the narrative review, accompanied by a description of how the literature search has been conducted and how the value of the identified studies has been evaluated. First, the research question is formulated and the inclusion and exclusion criteria are defined. A systematic search for the available evidence is then carried out. The next step involves selecting the relevant studies on the basis of the predefined criteria. The methodological quality/reliability of the included studies is assessed. The results of the selected studies are analysed and it may or may not be accompanied by a meta-analysis that quantitatively combines the results of the earlier studies. The advantage over a normal narrative review is that all the steps can be reproduced by others. The disadvantage is that an SR can be applied only to a restricted and well-defined question in a specific domain. It is also very time consuming and the added value is only significant if there are already a sufficient publications on the topic (Hooijmans, et al., 2010a; Kilkenny, et al., 2011). Value assessments of earlier studies, based on which these are either included or excluded, require in-depth knowledge and are sometimes subjective.

It can be difficult to perform an SR because many scientific articles do not provide all the necessary information, such as information on animal accommodation or the experimental design (Hooijmans et al., 2010a). A guideline for finding relevant animal studies, which facilitates the cataloguing and analysis of completed animal studies,

has recently been developed (Leenaars et al., 2011). Search filters have also been developed; one for Pubmed (Hooijmans et al., 2010b) and one for Embase (De Vries et al., 2011 en 2014).

3.2.3 Databases

Knowledge in the area of laboratory animal research and the value of different animal models can be made available through open-access databases. Researchers can consult these databases in the planning phase of projects to assist them in the planning phase of projects to choose the correct animal models or 3R alternatives that require as few animals as possible and lead to as little discomfort as possible. In this way, databases contribute positively to the 3Rs and can also play a role in the use of scientific knowledge (added value). Animal Welfare Bodies, Animal Ethics Committees and the CCD can also consult these sources of information to check whether the 3Rs are being optimally applied in the application for a project licence and during the conduct of animal procedures.

Examples of databases are the interspecies website (www.interspeciesinfo.com) with information on the anatomical, physiological and biochemical parameters of animal species and humans, the humane endpoints website (www.humane-endpoints.info) that helps to define exactly when an animal must be withdrawn from an experiment in order to avoid unnecessary discomfort, as well as the EURL-ECVAM (eurl-ecvam.jrc.ec.europa.eu/databases/database-on- alternative-methods-db-alm) and Altbib websites (toxnet.nlm.nih.gov/altbib.html) on alternatives.
Unfortunately, and hopefully temporarily, other databases are either not entirely up-to-date (such as the NORINA database and 3R guide) or are no longer available (such as the Animals-ZEBET website, the GoodCellCulture and the EURCA database) due to a lack of support. Better support of these types of databases would contribute towards the 3R policy.

3.2.4 Expert panels

Expert panels are formed by a number of experts from a particular field of research. They come together and write a document on current scientific understanding in relation to a specific scientific question, field, or disease model. The panel can make recommendations on prioritising research or on the possibilities of developing 3R alternatives. Internationally, expert panels often consist of scientific delegates from ministries or other public institutions and academics. The composition of these panels is usually broad and seldom includes less than 20 experts from different backgrounds but with expertise on the topic. Although individual members of an expert panel might not always be entirely impartial, the outcome of their joint opinion is regarded as being impartial and can serve as guidance for subsequent research decisions. Examples include WHO/IARC (on determining the carcinogenic properties of substances), FAO (JECFA, JMPR; monographs on the toxicity of substances), EFSA Panels (on the toxicity of additives and contaminants in food); the OECD (on nanotechnology and security), the ECVAM expert workshop on best practices for the control of vaccines (Hendriksen et al., 1994) and the SCHER Committee of the EU.

Expert panels can also play an important role in answering urgent scientific or societal questions on animal laboratory research and on what is and is not possible with regard to the 3Rs.

3.3 Dutch policy in relation to SoE

3.3.1 Grants

The Ministry of Economic Affairs has made around €5.8 million available for the research programme 'Meer Kennis met Minder Dieren' ('More Knowledge with Fewer Animals') of the Netherlands Organisation for Health Research and Development (ZonMw) for the period 2015 – 2017. The Organisation spends part of this funding on improving the knowledge structure. As described below, policy measures have focused on SR, with less attention for other forms of SoE. Among other things, ZonMw offers workshops under the 'More Knowledge with Fewer Animals' programme that provide hands-on training on the application of SRs to animal procedures. These workshops will be continued over the next three years, while training on location will also be provided. This organisation has also given financial support to Syrcle (an organization that promotes SR, see below) in order to provide guidance to people who wish to perform their own SR. Besides this financial support, Syrcle has received a grant from the Ministry of Economic Affairs to develop a manual and tools for performing SRs, guidelines and an e-learning module for use in laboratory animal science courses in the Netherlands.

3.3.2 Education

The laboratory animal science course has always paid attention to the design of an animal experiment and the optimal use of literature searches. This aspect was largely incorporated in an laboratory animal science assignment, for which students had to create and present an experimental study design, including carrying out a literature search, in supervised self-study. Besides this assignment, an SoE module has now been added in accordance with the EU Directive, which is structured in a variety of ways (e-learning, lectures and/or tutorials). SR is discussed in this module as one of the possible tools. This can be found in Article 5 and Appendix 6 of the Dutch animal procedures regulation (*Dierproevenregeling*) 2014.

3.3.3 Tabula Rasa research

In 2014, the Ministry of Economic Affairs asked Tabula Rasa to organise round-table discussions with researchers and laboratory animal experts from both universities and industry on the added value, opportunities and obstacles involved in applying SRs to laboratory animal research. The focus in this research was on SR and not other forms of SoE. Tabula Rasa concluded:

- Non-clinicians are hardly familiar with SR.
- SR has an added value but should not be made compulsory.
- SRs are most worthwhile when preparing for new lines of research that involve animal procedures, in retrospective studies, immediately before translation to clinical studies, in frequently used animal models and in choosing the most optimal methodology.
- Time, money, expertise and publishing opportunities are inhibitors in performing SR.

Tabula Rasa made the following recommendations in its report:

- Firmly establish SR in education and also increase familiarity with this amongst established researchers.
- Introduce incentives such as grants and encourage the inclusion of SR in large research programmes.

In March 2015, Tabula Rasa issued a second report on a questionnaire survey to provide insight into the experience with SRs and the need for knowledge and support. This survey was conducted amongst employees of biomedical and medical faculties. Although the questionnaire was completed by a large number of respondents who were well distributed among positions and subject areas, Tabula Rasa indicated that care needed to be taken with generalising the results because neither the entire population nor a representative sample could be addressed.

The main findings were:

- Many respondents were familiar with SR and recognised its importance in laboratory animal research.
- Reasons were also given for not encouraging the use of SR: the investment of time and questions for which SR is not the right choice.
- Respondents recognised the importance of paying attention to SR in education.
- Respondents found the application of SR in fundamental research to be more limited than in more applied preclinical research.
- The necessary investment of time plays a major role in the consideration whether to perform an SR.

3.4 Organisations

The concept of SR in laboratory animal research has been inspired by the Cochrane Collaboration. This organisation helps in health care decision-making by making information on the effectiveness of health care accessible in the form of SRs that are published online in The Cochrane Library. Cochrane reviews are mainly performed in human clinical studies.

Compared to its application in human medicine, SoE in laboratory animal research is still in its infancy. Fewer than 250 SRs of preclinical animal studies were published until 2010, while the number of Cochrane reviews of human clinical studies already totals almost 6,000 (Ritskes–Hoitinga et al., 2014).

Two leading research groups that support the application of SR in laboratory animal research are CAMARADES (Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies) and SYRCLE (Systematic Review Centre for Laboratory Animal Experimentation). CAMARADES regularly performs SRs of preclinical animal models for certain diseases. SYRCLE focuses on the development of methodology and guidelines, offers international education and training sessions and looks for collaborative ventures to promote the use of SRs in animal studies (Ritskes-Hoitinga et al., 2014).

In the United Kingdom, the organisation SABRE Research UK is committed to using SRs of animal studies in order to be able to determine their value in human applications. SABRE is independent of politics and the pharmaceutical industry and is driven by the patients' perspective.

3.5 Remarks on the use of SoE

3.5.1 Quality of studies and reports

Studies show that the design of animal experiment studies and the quality of reports is often far from optimal (Egan & Macleod 2014, Horn et al. 2001, Pound et al. 2004, Kilkenny et al. 2009). All too often, animal procedures that should have been blinded and

randomised are not conducted in this manner (Macleod et al., 2015). Examples of SRs that have revealed these shortcomings include reviews on the development of medication for strokes and multiple sclerosis (Macleod et al., 2008, Sena et al., 2010a; Van der Worp et al., 2010; Vesterinen et al., 2010). These shortcomings complicate the translation to humans. It has also been shown that the size of groups is not always well-chosen (Landis et al., 2012) and too few animals are sometimes used for proper statistical justification (De Vries et al., 2010; Vesterinen et al., 2010).

A number of observations need to be made in relation to this analysis:

- In exploratory studies, it is not always possible to predetermine the group size, because the anticipated effect size of an intervention is not yet known.
- The requirement of randomisation may lead to an increase in the number of animals in an experiment. For instance, if an additional experiment is planned on the basis of unexpected outcomes in a previously tested group of animals, the requirement of full randomisation may necessitate repeating the first experiment, leading to an increase in the number of laboratory animals used.
- In exploratory studies, blinding can lead to the consequences of an intervention being missed if these are not yet known (Steward & Balice-Gordon, 2014). An example of this is an exploratory anatomical study into the impact of treatment on several organs. Blinding can hinder the detection of the difference between the normal anatomical variation and an unexpected effect. If a significant effect is determined in a non-blinded analysis, this effect could be verified in a blinded analysis.

There are initiatives to improve the quality of reports in scientific publications, including the Gold Standard Publication Checklist (Hooijmans, et al., 2010a) and the ARRIVE guidelines (Kilkenny et al., 2011).

3.5.2 *Negative results*

It is easier to get positive results published than negative results, because positive outcomes are often more interesting. If something appears not to work, scientific interest in it is less than if a new mechanism or new medication, or the application thereof, is described. This leads to publication bias (Sena et al., 2010b); the chance of getting studies with negative outcomes published is lower compared to studies with positive outcomes. The effectiveness of medication can be overestimated as a result and this can, in turn, interfere with translation to humans (Smit et al., 2015, Ter Riet et al., 2012).

However, there are new options for publishing negative results and replications of earlier studies. Journals that provide scope for this include *BMC Research Notes*, *F1000 Research*, *Journal of Negative Results in BioMedicine*, *eNeuro*, *Journal of Pharmaceutical Negative Results*, *PeerJ*, *PLOS ONE* and *The All REsults Journals; biology*.
The Netherlands Organisation for Health Research and Development (ZonMw) also encourages the publication of negative results (http://www.zonmw.nl/nl/subsidies/subsidiekalender/detail/item/meer-kennis-met-minder-dieren-publiceren-negatieve-data/)

3.5.3 Professional confidentiality

Not all conducted animal procedures are published. Some of the outcomes of animal procedures may be covered by professional confidentiality agreements. For example. Due to the high level of competition, pharmaceutical companies do not indicate what developments they are working on in the preclinical phase. The high research, production and marketing costs, as well as the time that it takes to bring a medication to market, must namely be recovered during the period of a patent. Apart from the fact that there are relatively few publications with positive results from the industry, there is no insight into negative results obtained from animal procedures within the pharmaceutical industry. These studies mostly remain invisible to forms of SoE (De Vries et al., 2010).

3.6 Applicability of SoE in various scientific domains

Knowing what has been published is inherent to being a successful researcher. Researchers write reviews about their area of expertise and summarise current scientific understanding in their research field when writing scientific articles and applying for grants. It is not prudent to draw a strict dividing line between fundamental and preclinical research with laboratory animals, as much disease-related research relies on results from fundamental research and vice versa. Even so, the degree to which the different forms of SoE can be applied differs between these two research areas.

3.6.1 Fundamental research

In this field, writing narrative reviews is common, while there are little to no SRs available. Since fundamental research mostly involves new topics that are explored for the first time, performing SRs is not worthwhile. The Tabula Rasa research in 2014 therefore revealed little support among fundamental researches for SR (Swankhuisen & Smit, 2014). Databases with animal models can provide added value in the choice of an appropriate animal model for diseases or physiological functions.

3.6.2 (Pre)clinical/applied research

SoE can produce information that is relevant to whether to start or not to start a clinical study. Within this research, it is also important to distinguish between exploratory research and a later phase that lies close to when a new treatment is applied in the clinic (Kimmelman et al., 2014). The objective during the exploratory phase, for example, is to provide insight into the origin of a disease or to screen a larger series of potential therapeutic interventions with the aim of selecting one or a small number of new medications for further research. During this phase, it is difficult to determine what the ideal size of the laboratory animal group should be beforehand. Narrative reviews are mostly written in this phase. The added value of SRs is most evident when researchers have selected the most promising intervention and the expected effect is easier to determine. The file that is submitted to a Medical Ethics Review Committee (MERC) contains a summary of the relevant laboratory animal studies (Investigator's Brochure). However, even in this relatively late stage, there may still not be enough studies to perform an SR.

3.6.3 Regulatory research

The use of SoE, particularly in the form of a comprehensive narrative review, is generally applied within toxicology. This applies especially to substances from the food chain and chemical sector in respect of

which there is a lot of information from previous laboratory animal research. In these cases, a comprehensive narrative review, such as a monograph and sometimes an SR, can avoid unnecessary laboratory animal research.

In the first years of its existence, the European Food Safety Authority (EFSA) already called for far-reaching transparency and the systematic use of previously conducted toxicological research (SoE) in order to form a proper opinion on the safety of substances in our food. The terms 'evidence-based toxicology' and 'intelligent testing,' which both actually refer to narrative review, are commonly used in toxicology.

3.7 Analysis

SoE enhances the quality of future research and makes an important contribution to a proper study design. An analysis of the possible reasons why the outcomes of previous animal procedures have differed can provide insight into the quality of the animal model to be chosen, the likelihood of translation to the human situation and, if the research is aimed at human diseases, to the disease process itself (Steward & Balice-Gordon, 2014).

There are different forms of SoE. Narrative reviews, comprehensive or otherwise, are common in all scientific fields and form part of the scientific routine. SRs often cannot be used, as the preconditions cannot be met, for example because there are not enough related studies available. SRs are also more time consuming; according to the Cochrane Collaboration, SRs take at least twelve months and require a precisely defined question and in-depth knowledge for assessing the quality of previous studies. A good SR therefore requires close cooperation among researchers from the scientific domain of interest and other disciplines who can assist in ways that include tracking down the relevant studies (Swankhuisen & Smit, 2014). The usefulness of SRs in fundamental research questions and particularly in new research areas is restricted in view of the limited availability of relevant data. Limitations are also caused by failures in reporting research results, the non-publication of negative results and professional confidentiality agreements. Others forms of SoE include databases that contain data on animal models and can be used by researchers around the world, as well as the use of expert panels/ reviews. Although grants are available for SRs, it would be good to also open these grants to other forms of carefully documented SoE that can make a significant contribution to the 3R policy, such as databases and expert panels.

SoE is extremely important. It contributes towards the quality of the study design and prevents the unnecessary duplication of research. The precise chosen SoE form depends on the specific research question and available knowledge. NCad intends to adapt this position statement on SoE in the European context into a Code of Practice.

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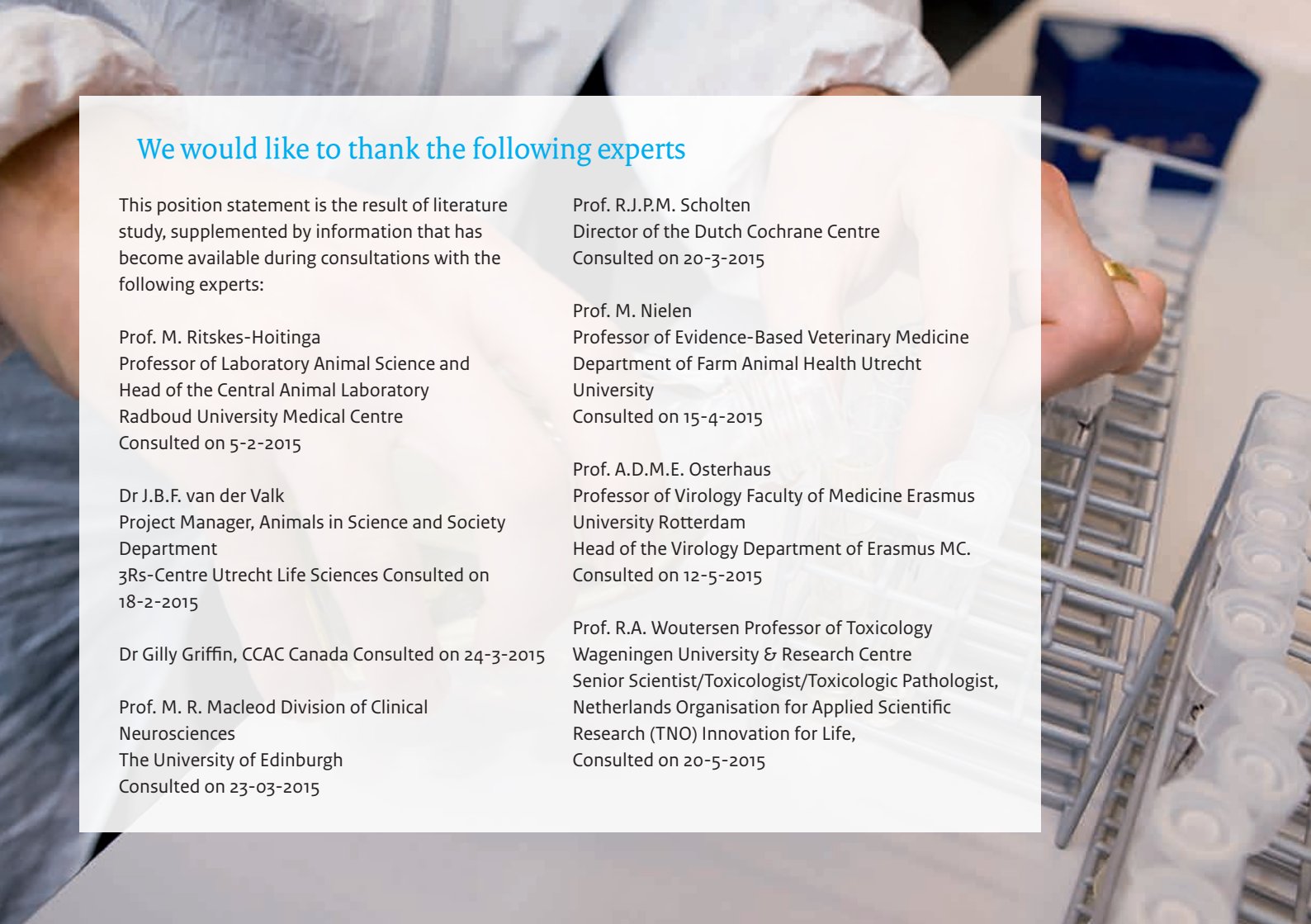

We would like to thank the following experts

This position statement is the result of literature study, supplemented by information that has become available during consultations with the following experts:

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This is a publication of the Netherlands National Committee for the protection of animals used for scientific purposes (NCad)
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2500 EK The Hague
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Publication date: April 2016
Publication no.: 201603EN

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