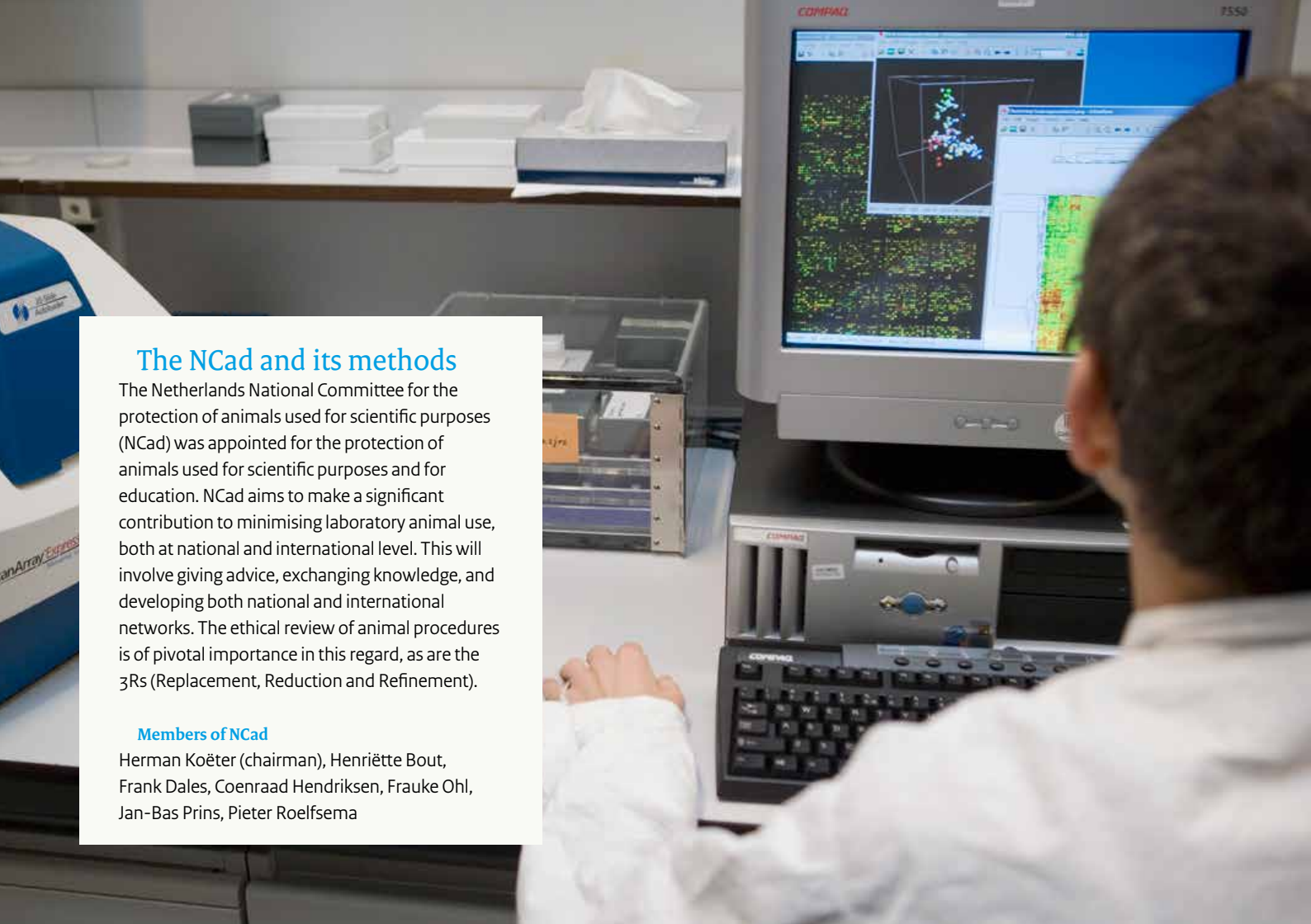
Indicators, management and utilisation of data for monitoring laboratory animal use and 3R alternatives, part 1

Advisory report, prepared by members of the Netherlands National Committee for the protection of animals used for scientific purposes (NCad) at the request of the Minister for Agriculture



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 purposes and for education. 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).

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Summary

In a letter dated 31 March 2015, the Minister of Agriculture (EZ) asked the National Committee for the protection of animals used for scientific purposes (NCad) to issue an advisory report on the management and use of data for monitoring laboratory animal use and 3R alternatives for the Reduction, Replacement and Refinement of laboratory animal use (taking due account of advisory reports and studies from the Netherlands and elsewhere). More specifically, the NCad was asked to divide its advisory report into two partial advisory reports (referred to as Part 1 and Part 2):

1. management and use of data on laboratory animal use and 3R alternatives; and
2. identifying any indicators that could contribute to a better understanding of facts and developments with respect to laboratory animal use and 3R alternatives, and which could be used for developing and directing policy.

The NCad's present advisory report meets the first part of the request for advice. The feasibility and cost-benefit analysis of management and use are highly dependent on the exact indicators used. For this reason, these aspects will be discussed in Part 2 of the advisory report which, it is expected, will be issued at the end of 2015.

The guiding principle of the advisory report is the Minister's ambition (as formulated in the Action Plan for Animal Procedures and Alternatives) to promote animal welfare and to minimise the number of animal procedures as much as possible. With regard to the management and use of data for monitoring laboratory animal use and 3R alternatives, the Minister of Agriculture received the following recommendation from the NCad.

1. The structured collection and provision of data

The NCad recommends compliance with government policy on open data, with regard to all information made available by the government on laboratory animal use, animal procedures, and 3R alternatives. Publication of such material is subject to the restrictions imposed by privacy sensitivity and the protection of intellectual property.

The NCad points out that, in this regard, Dutch practice goes further than is usual in Europe. Accordingly, in the interests of establishing a level playing field, it advises the Minister to commit herself to a European open data policy as well. The NCad would like to offer its services in tracking the impact of this open data policy on the competitiveness of researchers and companies.

The open data should be made available in the form of a central data warehouse that is publicly accessible via a website. Furthermore, the NCad recommends that this central data warehouse should also contain information provided by practitioners working in the field. The data sets contained in this data warehouse should be structured in a way that enables matrix connections to be established, and that enables data to be regrouped and analysed, such as:

- Data that is presented in an accessible manner and arranged into recognisable categories relating to laboratory animal use, including the purposes for which laboratory animals are used, the number and species of animals used, and the associated severity classifications;
- Categorised information about 3R activities related to the development and implementation of 3R alternatives, through the use of international online information sources and the application of evaluation methods, such as 'synthesis of evidence';
- In addition, parties working in the field must be encouraged to incorporate the following databases into the data warehouse.
- Information from establishment licensees about local 3R developments, based on indicators that will have to be defined in more detail by the NCad, in consultation with those working in the field. The legal option of ultimately making it mandatory to supply such data should be examined;

Information from licenced establishments in the Netherlands that are engaged (beyond the reach of the Animal Testing Act) in developing technologies or research strategies that can replace or reduce animal procedures.

Finally, the policy should take steps to harmonise activities in the field of data management and utilisation in Europe, focusing on a data warehouse at European level. This may ultimately lead to more efficient laboratory animal use and to progress in the development and implementation of 3R alternatives.

In the short-term, these measures will mainly contribute to transparency regarding laboratory animal use and 3R activities in the Netherlands. In the longer term, cooperation between licenced establishments and between researchers can be facilitated and the effects of measures made visible.

The NCad will advise on feasibility and phasing in the second part, and will examine the costs of setting up a data warehouse of this kind.

2. Making better use of available data

- Involve the Central Authority for Scientific Procedures on Animals (CCD) and the Netherlands Food and Consumer Product Safety Authority (NVWA) – based on their central role in the prospective and retrospective reporting of laboratory animal use – in setting up a central data warehouse;
- Make public funds for 3R research data available in the structured data warehouse;

Ensure that links can be established with information about laboratory animal use held in the existing databases. This must be done in a way that will make it possible to generate regular, detailed trend analyses of laboratory animal use in prioritised categories of research. The improved insight into laboratory animal use that this will deliver, together with the development and application of 3R alternatives, may result in the more efficient use of this information. It may also improve policy management and study design, while providing a better basis for the development and implementation of 3R alternatives.

3. Improving the accessibility of data

When using information from the data warehouse, modify the annual report on animal procedures and laboratory animals to provide insight (that is both accessible and explanatory in nature) into trends in 3R research and their impact on laboratory animal use;

- In this connection, include the following elements in the annual report on animal procedures and laboratory animals:
- A justification of 3R research that is financed from public funds, and of the results this has produced;
- Providing greater insight into the animal procedure policies of establishment licensees, their 3R activities, and the resultant output and impact;
- Data on trends in laboratory animal use, and 3R alternatives for statutorily prescribed research, to be supplied by the National Institute of Public Health and the Environment (RIVM). This is based on that organisation's pivotal position in Dutch 3R research for regulatory purposes and on its input in shaping the associated regulations;
- Appoint a party (or parties) to be responsible for a comprehensive annual report on laboratory animal use and 3R alternatives in the Netherlands and for periodic evaluations of laboratory animal use (to be appended to the above report) and 3R developments within prioritised research areas, their use in the Netherlands, the Netherlands' share in this, and expectations for the future.
- Require establishment licensees, each year, to demonstrate (based on a number of clear criteria) openness with regard to their laboratory animal policy (including their aspirations and dilemmas in this area) and to their efforts in relation to 3R alternatives.

  The NCad would like to offer its services in drawing up the requisite procedure in 2016, in collaboration with practitioners working in the field. An important consideration in this regard is that the quality and objectivity of information must be ensured by means of independent audit-based reviews.
- Assign establishment licensees the task of further developing the statutory duty[1] of Animal Welfare Bodies (IvDs) into a Code of Practice, with respect to encouraging the use of the 3Rs in licensed establishments. A working group (consisting of stakeholders from the field) can be set up for this purpose, with the NCad acting as a facilitator. The Code of Practice will offer IvDs guidelines on how to establish and maintain an "accounting system" for 3R activities within the licenced establishment.

Keywords

Monitoring, open data, transparency, central data storage, 3R, laboratory animal use, data warehouse

Contents

1. Introduction

In the Netherlands, laboratory animals are used for a variety of research objectives, ranging from basic and applied research, to regulatory testing and education. Some of these laboratory animals are used for breeding. In addition, direct and indirect efforts are being made in the area of 3R activities: the development and implementation of 3R alternatives for the Replacement, Reduction and Refinement of animal procedures. Here, the development of 3R alternatives is often a spin-off, rather than an end in itself, so it is not always regarded in terms of 3R alternatives. This means that there is extensive information on laboratory animal use and 3R alternatives, spanning many different areas of science, and that it is not always immediately visible.

In line with European registration requirements, the Netherlands Food and Consumer Product Safety Authority (NVWA) reports in "Zo doende" (its annual review of animal procedures and laboratory animals) on the number of animals used in (or held for the purposes of) animal experimentation in the Netherlands, and on the purposes for which these animals are used. This report's consistent use of indicators makes it possible to draw comparisons between consecutive years.
Nevertheless, the information reported in this way gives an incomplete picture. The following gaps have been identified:

- While the available information may indeed be an indication of various current trends and developments, no predictive value can be attached to it;
- There is only a limited amount of information available concerning "research efficiency" (the yields from animal experimentation) or research into 3R alternatives for society;
- It neither gives details of the state of the art with regard to the development of 3R alternatives, nor of the prospects for the various research areas in this respect;
- Nor does it always include details of the actual use of 3R alternatives (especially as Replacement), as these are not covered by animal registration in many cases;
- Similarly, the international context in which Dutch laboratory animal use and 3R activities (in the area of the development and implementation of 3R alternatives) occur has not been placed sufficiently in the limelight.

In order to develop a broadly supported laboratory animal policy that centres around the 3Rs, it is important to gain an insight into developments in both laboratory animal use and 3R alternatives. The Minister for Agriculture has asked the NCad to issue an advisory report on the management and utilisation of all available information concerning animal procedures and 3R alternatives. Monitoring such developments may provide additional insight into sporadic events and trends, while meeting society's need for transparency and openness. Additionally, monitoring can contribute to a more informed choice of research model, and thus to a quality improvement in research ("lessons learned"). Finally, policy development can use monitoring results to assess and direct

regulations and policies. In the Netherlands, various information sources are available for the purposes of monitoring.

This first part of the requested advisory report provides guidelines for a monitoring system that is deemed to be both manageable and effective. The guiding principle here is that some things that are important in terms of improving our understanding, can not be measured. Conversely, some of those things that can be measured are not important in terms of improving our understanding of developments in laboratory animal use and in the development and implementation of 3R alternatives[2].

Details of previous studies and reports on this topic were used in preparing this advisory report. In addition, interviews were conducted with representatives from relevant organisations, both in the Netherlands and elsewhere. In the context of the societal expert group on animal procedures and alternatives (MEDA), representatives of community groups have also contributed. Appendix 1 lists the names of the experts and parties that were consulted. The views of each of the community groups consulted on this topic are presented in Appendix 2.

2. Request for advice

In a letter dated 31 March 2015, the Minister for Agriculture (EZ) asked the NCad to issue an advisory report on the management and utilisation of data for monitoring laboratory animal use and 3R alternatives (taking due account of advisory reports and studies from the Netherlands and elsewhere). The NCad was also asked to identify any indicators that could contribute to a better understanding of developments with respect to 3R alternatives and animal procedures.

In drawing up its advisory report, the NCad was asked to focus on the following aspects regarding developments in the field of animal procedures and 3R alternatives:

- Making better use of available data, and improving its accessibility;
- Listing any gaps;
- Identifying indicators;
- Listing and prioritising the main short-term and long-term objectives of a centralised data storage system;
- Giving details of the feasibility of each of these objectives;
- Making a corresponding cost–benefit analysis.

The NCad was asked to publish its advisory report in two parts:

1. management and utilisation of data on laboratory animal use and 3R alternatives; and
2. identifying any indicators that could contribute to a better understanding of facts and developments with respect to laboratory animal use and 3R alternatives (such as revealing any duplications) and which could be used for developing and directing policy. The

feasibility and cost–benefit analysis of monitoring are highly dependent on the exact indicators used. Thus, the topics of "feasibility of objectives" and "cost–benefit analysis" will also be discussed in the second partial advisory report. The NCad aims to complete this part at the end of 2015.

3. Advisory report

The NCad's present advisory report meets the first part of the request for advice. The suggestions and recommendations concerning the structured collection and provision of data, the better utilisation of available data, and improving the accessibility of data, focus on the two themes that have been identified: laboratory animal use (animal experimentation, including the use of animals for education and breeding) and the development and application of 3R alternatives.

The guiding principle of the advisory report is the Minister for Agriculture's aspiration (as formulated in the Action Plan for Animal Procedures and Alternatives[3]) to promote animal welfare, to minimise the number of animal procedures as much as possible, and to promote transparency and openness. Through active dialogue and cooperation (both substantively and financially), efforts will be made to jointly develop, share and apply knowledge. The Minister for Agriculture describes the role of policy in this endeavour as not purely legislative, it will also involve setting the agenda, directing activities, providing encouragement and facilitating.

The NCad has formulated the following recommendations and suggestions. A substantiation and explanation of Part 1 of the advisory rt will follow.

3.1. The structured collection and provision of data

The information reported annually by various parties gives an incomplete picture of laboratory animal use and, in particular, developments in the area of 3R alternatives in the Netherlands. Against this background, the NCad advises the Minister for Agriculture to:

1. Comply with government policy on open data[4], with regard to all information made available to the government on laboratory animal use, animal procedures, and 3R alternatives. Publication of such material is subject to the restrictions imposed by privacy sensitivity and the protection of intellectual property.

The NCad points out that, in this regard, Dutch practice goes further than is usual in Europe. Accordingly, in the interests of establishing a level playing field, it advises the Minister for Agriculture to commit herself to a European open data policy as well. The NCad would like to offer its services in tracking the impact of this open data policy on the competitiveness of researchers and companies.

2. Encourage other parties to independently and actively disclose any of their data on animal procedures and 3R alternatives that has not already been shared via the government;
3. Based on a data warehouse[5], set up a free, publicly accessible website for the central storage of data on laboratory animal use and 3R activities that enables matrix connections to be established and data to be regrouped and analysed;

4. See to it that datasets in the data warehouse are efficiently structured, i.e.:
   - Easily searchable, presented in an accessible manner and arranged into recognisable categories relating to laboratory animal use, including the purposes for which laboratory animals are used, the number and species of animals used, and the associated severity classifications;
   - Categorised information about 3R activities, through the use of international online information sources and the application of assessment methods, such as "synthesis of evidence"[6];
5. Encourage establishment licensees to supply details about local 3R developments, and about their policies and aspirations, based on indicators that will have to be defined in more detail by the NCad, in consultation with those working in the field. Examine the legal options for ultimately making it mandatory to supply such data. This could involve making accreditation of the licensed establishment in question conditional on the publication of an annual report containing such information. Those non-licensed establishments in the Netherlands that are engaged in developing technologies or research strategies that can replace or reduce animal procedures (but which, with regard to their company operations, do not fall under the Dutch Experiments on Animal Act) should also be encouraged to do so.
6. Use the policy to take steps to harmonise activities in the field of data management and utilisation in Europe, focusing on a data warehouse at European level. This may ultimately lead to more optimal laboratory animal use and to progress in the development and implementation of 3R alternatives.

3.2. Making better use of available data

The structured collection and provision of data on laboratory animal use and 3R activities will contribute, in a direct sense, in a limited way to the promotion of animal welfare and to minimising the number of animal procedures. However, the improved insight into laboratory animal use that this will deliver, together with the development and application of 3R alternatives, may well result in the more efficient use of this information. It may also improve the management of policy and regulations by means of policy development, while providing a better basis for the development and implementation of innovative 3R alternatives, with the bonus of a quality improvement in research.

Accordingly, the NCad advises the Minister for Agriculture to:

7. Involve the Central Authority for Scientific Procedures on Animals (CCD) and the Netherlands Food and Consumer Product Safety Authority (NVWA) – based on their central role in the prospective and retrospective reporting of laboratory animal use – in setting up a central data warehouse;
8. Also get public 3R research funds involved to make data available in the structured data warehouse;
9. Ensure that links are established with information about laboratory animal use held in existing databases. This must be done in a way that will make it possible to generate regular, detailed trend analyses of laboratory animal use in prioritised categories of research (e.g. by research area, basic and applied research, regulatory research, disease studied, specific species).

3.3. Improving the accessibility of data

Additional activities are needed to find hidden information about laboratory animal use and, in particular, 3R alternatives, and to make this accessible in a user-friendly way.

Accordingly, the NCad advises the Minister for Agriculture to:

10. Use information from the data warehouse to modify the annual report on animal procedures and laboratory animals to provide insight (that is both accessible and explanatory in nature) into trends in 3R research and their impact on laboratory animal use;
11. In this connection, include the following elements in the annual report on animal procedures and laboratory animals:
    - A justification of 3R research that is financed from public funds, and of the results this has delivered (output and impact);
    - Provide greater insight into the animal procedure policies of establishment licensees, including their 3R activities, and the related output and impact;
    - Data on trends in laboratory animal use, and 3R alternatives for research in compliance with regulatory requirements, to be supplied by the National Institute of Public Health and the Environment (RIVM). This is based on that organisation's pivotal position in Dutch 3R research for regulatory purposes and on its input in the process of shaping the associated regulations;
12. Appoint a party (or parties) to be responsible for a comprehensive annual report on laboratory animal use and 3R alternatives in the Netherlands and for periodic assessments (to be appended to the above report):
    - Assessments (e.g. in the form of expert workshops or expert symposia) of laboratory animal use within prioritised research areas and the implications of these developments in the Netherlands. Based on this, projections can be drawn up;
    - Assessments (e.g. in the form of expert workshops or expert symposia) of trends in the development and implementation of 3R alternatives, and the Netherlands' contribution in this regard. Based on this, projections can be drawn up;
13. Require establishment licensees, each year, to demonstrate (based on a number of clear criteria) openness with regard to their laboratory animal policy (including their aspirations and dilemmas in this area) and to their efforts in relation to 3R alternatives. The NCad would like to offer its services in drawing up the requisite procedure and criteria in 2016, in collaboration with the research community. An important consideration in this regard is that the quality and objectivity of information must be ensured by means of independent audit-based reviews carried out by independent third parties.
14. Assign establishment licensees the task of further developing the statutory duty[7] of Animal Welfare Bodies (IvDs) into a Code of Practice, with respect to encouraging the use of the 3Rs in licensed establishments. A working group (consisting of stakeholders from the field) can be set up for this purpose, with the NCad acting as a facilitator. The Code of Practice will offer IvDs guidelines on how to establish and maintain an "accounting system" for 3R activities within the licensed establishment.

4. Substantiation of the advisory report

This section presents further substantiation for the above suggestions and recommendations, presented by the NCad, on the management and utilisation of data on laboratory animal use and 3R alternatives. In this connection, use was made of existing studies and reports on the topic of information management and information utilisation. Discussions were also held with a number of expert parties. A summary of these procedures is given in Appendix 1. Details of the information sources identified and the system used in this context are described in section 5.

4.1. The structured collection and provision of data

Collecting, managing and providing information on laboratory animal use and 3R alternatives is important for the following reasons:

Short term:

- it provides insight into laboratory animal use in the Netherlands (e.g. number, species, objectives, techniques used, proportion of genetically modified animals, percentage of animals sacrificed before use in breeding programmes or animal procedures) and into activities in the area of 3R alternatives to animal procedures (e.g. availability, actual use);
- it provides insight into laboratory animal use that is enshrined in regulations in the Netherlands, Europe and elsewhere, such as quality control (e.g. vaccines), safety (e.g. chemicals and food additives) and efficacy (e.g. drugs and pesticides);
- in this way it contributes to the social desire for greater transparency on these fields, e.g. in trends that translate into a decline in laboratory animal use;
- it provides an opportunity for scientific, ethical and social dialogue on the desirability, necessity and usefulness of laboratory animal use and 3R alternatives.

Longer term:

- it highlights developments and trends in laboratory animal use and 3R alternatives; by creating links between databases or other information sources (at national and international level) it can make connections (e.g. developments in science and society that can explain shifts in laboratory animal use);
- by creating improved insight into laboratory animal use and 3R activities, it can initiate collaboration between licensed establishments, avoid any unnecessary duplication of animal experimentation and make it possible to generate more knowledge with fewer animals; the unique position of the CCD will enable it to assist in this;
- it can be a management tool for policymakers and legislators, and it can highlight the impacts of policy and legislation;

The desire for greater transparency in animal procedures is embedded in Directive 2010/63/EU which, in the Netherlands, has been implemented in the Dutch Experiments on Animals Act (Wod) and its underlying regulations. In 2008, a number of Dutch licensed establishments signed the Animal Experiments Openness Code[8].

This document was drawn up by the Royal Netherlands Academy of Sciences (KNAW), the Association of Universities in the Netherlands (VSNU) and the Netherlands Federation of University Medical Centres (NFU) with the aim of "achieving non-obligatory openness and dialogue about animal procedures through self-regulation". In a broader sense, the pursuit of open data is enshrined in the EU's Horizon 2020 "Big Data Value Chain[9]". At national government level, this has been partially implemented through the Dutch National Data portal.[10] As yet, however, this data portal contains no details on laboratory animal use in the Netherlands.

The objective and target group of a centralised data storage system dictate both the type of data being input, and the way in which this is done. It is unrealistic to expect that the creation of a widely accessible centralised data storage system will cater fully to both the societal desire for transparency and to the needs of scientific researchers and any other interested parties, such as policy officers. The focus of the centralised data storage system, as presented in this advisory report, is on enhancing our understanding of laboratory animal use in the Netherlands and of activities in the area of 3R alternatives to animal procedures. This is primarily a response to societal desires, but it also provides a guideline for scientific researchers, in their efforts to expand our knowledge while using fewer animals.

Numerical data on laboratory animal use (statistics on planned and past laboratory animal use, including the species and number of animals used for various research purposes, and the associated severity classification) is particularly compatible with a centralised data storage system in a data warehouse. In addition, data from different databases is linked and made available at a central location, thus enabling data integration. It should be noted that currently available data on laboratory animal use in the Netherlands is already concentrated into a limited number of sources. Being quantitative in nature, these can easily be linked together. The available data and information sources are explained in more detail in Appendices 3 and 5.

The NCad will advise on feasibility and phasing in the second partial advisory report, and will examine the costs of setting up a data warehouse of this kind. An initial – conservative – estimate is that a data warehouse will require substantial investment, depending on the aspirations involved.

The initial, potential candidates for data warehouse sources are the CCD (the review and potential licensing of project applications prior to laboratory animal use) and the NVWA (the annual registration of laboratory animal use for the purposes of its "Zo doende" annual review of animal procedures and laboratory animals). In addition, as part of their statutory duties, establishment licensees' IvDs hold data that is of added value in terms of identifying trends in laboratory animal use and 3R alternatives. Both the CCD and the IvDs were established under the revised Dutch Experiments on Animals Act. Accordingly, they can make data available that has been collected since December 2014. The NVWA has more historical data (from 1978 onwards). Other sources of information for monitoring purposes are of secondary importance, as they have limited added value. An exception to this is a programme which monitors data in the literature on laboratory animal use in the

Netherlands for trends and – where appropriate – by conducting periodic syntheses of evidence.[11]

Information regarding 3R alternatives is very fragmented and often qualitative in nature, thus it does not easily lend itself to data collection and analysis. To some extent, information of this kind is not recognised as such, or it may even be hidden entirely, as explained in sub-section 4.3. For example, developments often occur within licensed establishments that – beyond the reach of the Wod and often without the use of animals – are engaged in the development of innovative techniques that could reduce or replace animal procedures, such as Organ-on-a-Chip. There is no current list of such establishments in the Netherlands.

Open access to largely hidden, descriptive information about 3R developments will be especially useful if this data is structured, e.g. by categorisation based on research area, species or clinical picture. However, it could also be based on keywords, such as stage of development or objective (e.g. which of the 3Rs). In addition, periodic assessments (e.g. involving synthesis of evidence studies in specific research areas) could also be of substantial added value in this regard.

4.2. Making better use of available data

Aside from being classified by research area, the database of registration data on Dutch laboratory animal use (NVWA) also includes information on the degree of distress/discomfort experienced by the animals used. Linking these two variables within the data warehouse can provide information on the extent of laboratory animal welfare compromises in a specific research area (e.g. cardiovascular research). Links of this kind would make it possible to highlight developments over time, as well as shifts or trends. This also applies to the combination of the CCD's prospective data on expected/planned laboratory animal use in research projects with the NVWA's registration data on actual laboratory animal use.

Experts in the relevant fields can then further identify and explain such shifts in quantitative data. Quantitative data can, after all, be influenced by such factors as changes in the definition of the terminology used (e.g. the definition of the term "animal procedure") and differences in interpretation between those who are submitting the data. Other factors may also be involved, such as technological developments and strategic choices (including strategic policy choices). In addition, trends and developments in laboratory animal use may be based on important ethical considerations. For instance, efforts to reduce and refine laboratory animal use are plagued by conflicting objectives. The objective of reducing welfare compromises for individual animals can result in the use of additional animals, each experiencing less distress/discomfort, rather than fewer animals each experiencing more distress/discomfort.

Targeted assessments should be carried out on relevant quantitative information from literature databases that are to be included in the data warehouse. Here, the Dutch situation is not viewed in isolation, but is seen in a broad international context. Such synthesis of evidence studies can be used to identify international trends in laboratory animal use. The assessment of prioritised research areas or research

programmes may provide more specific insight into the relevance and contributions of animal procedures, developments in the area of 3R alternatives, future prospects, and a roadmap to launch the required changes/developments. Funds for 3R research can play a part in this, by making project data (such as progress reports and final reports) available in the data warehouse.

By conducting a meta-analysis of project data from prioritised research areas, as part of an assessment (by means of a synthesis of evidence study), results from individual published animal procedures can be combined (for some of those areas of research, at least), leading to new knowledge.

Various parties in the Netherlands can establish links and combinations of data, and make the resulting knowledge available. Only a few parties in the Netherlands are capable of performing highly complex assessment studies or systematic review studies in the area of animal procedures and 3R alternatives.

In the area of regulatory research, an assessment (based on the legal frameworks) can be carried out to determine whether methods for replacing animal procedures are actually implemented. The RIVM has a pivotal position in Dutch 3R research for regulatory purposes and provides input used in the process of shaping the associated regulations. A national knowledge network will be established in the area of regulatory research (and the associated 3R developments). Launched by the RIVM, this network could serve as an important information source for the data warehouse.

4.3. Improving the accessibility of data

Like animal procedures, 3R research is funded from a range of different sources. The results of this research are reported, used and disseminated in different ways. As a consequence, information about 3R activities is often fragmented or even remains hidden in the literature. Thus, it may be a long time before the yields of such research can be identified. The objective of improving the accessibility of data is to make this information accessible, in a user-friendly way, by setting up a publicly accessible website (in conjunction with the data warehouse), featuring structured links to information sources.

The various 3R-specific databases, journals and organisations are important sources of information on 3R alternatives. Based on the highly diverse information that is combined in this way, analyses (including statistical analyses) and assessments can be conducted to provide insight into the state of the art in a given area of research. Prioritisation could be carried out by applying criteria such as types of research involving severe distress/discomfort or substantial laboratory animal use, or specific research programmes. The options in this regard have already been discussed in sub-section 4.2. The advantage of an approach like this is that part of the hidden information on 3R alternatives is also made accessible.

Hidden information about 3R developments is encountered in the following situations:

- 3R development that is derived from research focused on a different target. Within projects, changes are routinely made to in vitro models, in animal models or in production processes that, directly

or indirectly, lead to a reduction or refinement of laboratory animal use (see Appendix 4 for some examples). This "3R spin-off" is not recognised as such and, therefore, is not cited as such in publications, which makes it difficult to find;
- 3R research that generates sound results that are either negative or neutral in nature. This leads to a situation in which information that is relevant to 3R development is not published;
- Competitive research where confidentiality (IP[12]) is involved, as in private research institutions and certain studies conducted by public research institutions.

Sound results that are either negative or neutral in nature are only published to a limited extent, although some funding organisations such as the Netherlands Organisation for Health Research and Development (ZonMw) do encourage the publication of such results. In addition, more and more online scientific journals are providing the option of including raw research data, including sound negative or neutral results from projects (or aspects thereof), in appendices.

Additional information from establishment licensees about laboratory animal policy, their aspirations in this area and their efforts to develop and use 3R alternatives (also in relation to their total investment in animal procedures) has added value for identifying trends in laboratory animal use and 3R alternatives. Information provided in the past to the NVWA, in the context of the annual registration of laboratory animal use, offers too little guidance in this regard. Thus, the second NCad partial advisory report will propose the use of robust indicators that can serve as monitoring guidelines. The possibility should be explored of requiring establishment licensees (in the context of their establishment license[13]) to keep records and to provide information (in the annual report) concerning criteria determined by an independent party and concerning their policies, aspirations, objectives and progress in the areas of laboratory animal use and 3R alternatives. The NCad would like to offer its services in drawing up the requisite procedure and criteria in 2016, in collaboration with the research community. An important consideration in this regard is that the objectivity of information must be ensured (by means of independent audit-based reviews carried out by independent third parties).

This kind of commitment to openness creates awareness and a positive dynamic among establishment licensees. At the same time, it requires a harmonised approach and a verification of the information supplied by an expert in the relevant fields. An obvious initial step here would be to designate the Animal Welfare Bodies of the various licensed establishments.

5. Inventory of information sources on laboratory animal use and 3R alternatives

Appendix 3 lists data that is already available for laboratory animal use (Part A) and for 3R alternatives. Both at the level of "input" (type of establishment licensee and the way in which research is funded) and "output" (the products of projects), various parties record data on laboratory animal use and/or 3R alternatives.

Laboratory animal use within the various types of establishment licensees is financed from public (direct or indirect funding) and private (charities, internal funding and contract research) funds. All laboratory animal use for research, education and breeding purposes requires a project licence which, following the recommendation of an Animal Ethics Committee (DEC), can be granted by the CCD. The Animal Welfare Bodies are involved in the application for a project licence and, following licensing, in planning the animal procedures. The output of animal experimentation is knowledge, including knowledge of the animal models, patents, education and literature used. It also includes statistical reports on laboratory animal use, as reported annually to the NVWA.

3R research is also funded from a wide variety of public and/or private funds and budgets (direct, indirect and contract funding). Depending on whether animals (or donor animals, for supplies of cells or organs) are used, 3R research may or may not take place within the framework of the Wod and the associated licensing by the CCD. Output in terms of products and sources is highly diverse.

The parties listed in Appendix 3 who could serve as a source of data on laboratory animal use and/or 3R alternatives are briefly described in Appendix 5. This gives details of each information source's options and limitations, in terms of monitoring laboratory animal use and 3R alternatives.

6. International activities

In the framework of this advisory report, the situation in various countries with efficiently operating registers for laboratory animal use and/or 3R alternatives has been examined to determine whether, and – if so – to what extent, they also monitor trends, developments and effects.

To that end, organisations in Germany (ZEBET[14]), Canada (CCAC[15]), the UK (Home Office[16] and NC3Rs[17]) and Denmark (Dyreforsøgstilsynet[18]) have been contacted. Each of these organisations has clearly presented itself in association with this topic.

Inquiries have revealed that:

- in most cases, laboratory animal use is registered and any trends associated with such use are examined. This meets the legal requirement laid down in Directive 2010/63/EU;
- there is no data processing involving the linkage of databases from the registry (at national, European or intercontinental level);

- virtually none of the countries surveyed conducted registration and monitoring of the impact of 3R activities on laboratory animal use in terms of a reduction in (or refinement of) such use;
- Denmark carries out 3R registration based on the project licence, but (as yet) this process is still not being monitored. However, they are working on Codes of Practice;
- Germany and Canada have previously discussed setting up animal procedure related and 3R related data monitoring systems but, as yet, no action has been taken in this regard;
- only the United Kingdom publishes an annual Delivery Plan Report, which – in connection with policy arrangements – includes a qualitative report on 3R activities.[19] In this report, the Home Office shows how, in a limited number of government-funded research projects, policy proposals are transformed into 3R developments, and what impact (mainly in qualitative terms) this has had on laboratory animal use.

A 3R-monitoring system has been set up by the UK's National Centre for 3Rs (NC3Rs[20]), which funds 3R research and is closely involved in the further sections of the chain, right up to implementation. In this system, the input (activities and resources) is related to the output, which draws a distinction between "outcomes" (e.g. articles and lectures), "interim impacts" (e.g. a change in policy and practice) and "mature impacts" (a Replacement, Reduction and Refinement in laboratory animal use). The system is specifically designed to monitor 3R projects that are funded by NC3Rs and which are, therefore, subject to implementation limitations at national level. Such a system can, indeed, only be used to monitor developments that have been earmarked as 3R research. Accordingly, the 3R spin-off of any developments that are not earmarked as such will not be visible here.

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Appendix 1: Experts and parties consulted

Details of the literature consulted when drawing up this advisory report are given in section 7. Discussions were also held with representatives of organisations in the Netherlands who manage and use information about animal procedures and 3R alternatives:

- NVWA: Noortje Reeuwijk, Jeroen Peijs
- Central Authority for Scientific Procedures on Animals
- Animal Welfare Bodies (IvDs): Pascalle van Loo, Pieter Verbost, Willem Kamphuis
- ZonMw: Erica van Oort

- SYRCLE: Merel Ritskes-Hoitinga, Marlies Leenaars
- RIVM: Anne Kienhuis

The following representatives of relevant international organisations were asked about possible comparable activities:

- Home Office, United Kingdom: Judy MacArthur Clark, Head, Animals in Science Regulation Unit
- NC3Rs, United Kingdom: Mark Prescott, Head, Research Management and Communications
- Canadian Council on Animal Care (CCAC), Canada: Gilly Griffin, Director of Standards
- ZEBET, Germany: Barbara Grune, head of ZEBET Database on Alternatives to Animal Experiments on the Internet (AnimAlt-ZEBET) and Information Procurement
- DyreforsØgstilsynet (Animals Experiments Inspectorate), Denmark: Peter Bollen, Head of Biomedical Laboratory Unit, University of Southern Denmark

Finally, at a meeting held on 5 June 2015 in The Hague, the following community groups provided input for the advisory report (in the framework of the societal expert group on animal procedures and alternatives (MEDA)): BPRC, KNAW, NV-DEC, NVP, NFU, TRAIN, Wil Research, the professional group of animal welfare officers, HollandBio.

Appendix 2: Recommendations arising from the consultation of community groups

During a meeting held on 5 June 2015 in The Hague, BPRC, KNAW, NV-DEC, NVP, NFU, TRAIN, Wil Research, the professional group of animal welfare officers, and HollandBio provided input for the advisory report (in the framework of the societal expert group on animal procedures and alternatives (MEDA)):

These groups were offered an opportunity to clarify this input in writing after the meeting, but none of them opted to make use of it. The NCad distilled various recommendations from audio recordings made during the meeting. These were then presented to the respective groups for their approval. The recommendations, which were originally in Dutch, were signed and approved by these groups, per topic, and are shown below, translated into English. In each case, an indication is given of whether that particular recommendation was taken into account in the NCad's advisory report. Where that is not the case, brief details are given of the reason for this.

The structured collection and provision of data

Biomedical Primate Research Centre (BPRC)

- Engage the services of specialist associations working in specific areas of research for the purpose of identifying and interpreting trends (taken into account in the advisory report)

Royal Netherlands Academy of Sciences (KNAW)

- Identify the target group for centralised data storage in advance (taken into account in the advisory report)
- Keep in mind the trend that, when setting objectives for their research, researchers' choices are influenced by the need to qualify for funding, as well as by political and societal pressure. Ultimately, only a very small proportion of these objectives are actually achieved (taken into account in the advisory report)

Netherlands Association for Laboratory Animal Science (NVP)

- Determine whether the substantial efforts required do indeed achieve the intended yield (no, will be addressed in partial advisory report 2)
- With regard to data storage, focus on Replacement and possible Reduction, as society is mainly interested in 3R trends that translate into a decline in laboratory animal use (taken into account in the advisory report)

Netherlands Federation of University Medical Centres (NFU)

- Make it clear that the storage of data on laboratory animal use and 3R alternatives mainly involves laboratory animal use and Replacement alternatives (taken into account in the advisory report)

Three Rs Alternatives Initiating Network (TRAIN)

- Decide in advance the purpose of data storage and the target group involved (including accessibility), as these will determine the type of data involved and the way in which this can be collected (this is especially true of data that the industry is persuaded to make available) (taken into account in the advisory report)

Wil Research (on behalf of the industry)

- Give due consideration to the aspect of confidentiality, as this is a major constraint on such a centralised data storage system (taken into account in the advisory report)
- Examine trends and developments in the international context (taken into account in the advisory report)

Making better use of available data

Biomedical Primate Research Centre (BPRC)

- Store the data in categorised form, to make it possible to give an impression of each individual category (e.g. industry versus academia) (taken into account in the advisory report)
- Bear in mind that 3R developments in some areas of research are more easily identified than those in other areas (taken into account in the advisory report)

Royal Netherlands Academy of Sciences (KNAW)

- For the purposes of data storage and monitoring, a clear definition of 3R alternatives is essential, in order to avoid differences in interpretation (yes, to be taken into account in partial advisory report 2)

Netherlands Association for Laboratory Animal Science (NVP)

- Get the academic community to provide (via their Animal Welfare Bodies) greater insight into the Replacement alternatives (and a degree of Reduction), but keep in mind that Animal Welfare Bodies' primary focus is research in which animals are used, so it may not be possible for them to provide such information for the entire research field (taken into account in the advisory report)

Netherlands Federation of University Medical Centres (NFU)

- Set up clear frameworks for the data storage system, e.g. in terms of the type of development upon which it will focus (technological trends, as well as factors affecting research, such as funding and policy) (taken into account in the advisory report)
- Examine trends and developments within the Dutch field of research, in the international context (taken into account in the advisory report)

- Make use of qualitative data, especially in the area of animal welfare, to identify quantitative data on laboratory animal use (such as the number of animal procedures, the number of laboratory animals, and possible reduction of laboratory animal use), because the figures are influenced by a variety of factors, such as the definition of terminology (taken into account in the advisory report)
- Combine crude registration data with prospective data and make this available in anonymised form (taken into account in the advisory report)
- Appreciate that there is a clear difference between regulatory research and academic science. The former is highly oriented on methodology, and there is an openness to discussions about 3R methods. In the area of academic science, however, the issue of how scientific questions are asked and how they can best be answered should ideally be examined at a higher level of abstraction (taken into account in the advisory report)

Three Rs Alternatives Initiating Network (TRAIN)

- Start with regulatory research, as that gives you the option of using legal frameworks to check whether 3R alternatives are actually being implemented (taken into account in the advisory report)
- Ensure that there are sufficient positive stimuli and options to elicit information about 3R alternatives from industry (often very large international companies) (to be taken into account in partial advisory report 2)
- Bear in mind that, in academia, it may be easier to gain insight into trends by approaching researchers on a "sector by sector" basis (e.g. cardiovascular disease), since those who work with animal models are often in contact with researchers who work in vitro (taken into account in the advisory report)

Wil Research (on behalf of the industry)

- Keep in mind which data is relevant to society (taken into account in the advisory report)
- Choose an approach based on the issue of whether 3R alternatives are being used ("we use test x") or as a derivative of the savings achieved ("Previously, we carried out 100 tests a year, each of which involved three rabbits. Now we use in vitro tests, which saves 300 rabbits each year") or a combination of both (yes, will be explored in further detail in partial advisory report 2)
- Ensure that the NVWA includes in its database details of developments and trends in laboratory animal use and 3Rs within individual licensed establishments that are supplied to them on an unsolicited basis (taken into account in the advisory report)
- Use the replacement of regulatory testing (totalling around 25% of laboratory animal use in the Netherlands) as a specific reference point to show that replacement alternatives are being used on a large scale (taken into account in the advisory report)

Professional group of animal welfare officers

- Based on society's desire for transparency, provide insight into quantitative data (numbers) relating to laboratory animal use. However, one should also clarify the usefulness of such laboratory animal use (e.g. by working out how many of the animal procedures carried out in a year resulted in scientific publications) (taken into account in the advisory report)
- Engage the services of the internal Animal Ethics Committees of major international companies (industry), whose members include individuals with a knowledge of the 3Rs, to obtain details of their 3R activities (taken into account in the advisory report)

HollandBio

- When designing data storage systems, it is important to work out exactly what you want to get out of them when they are up and running, as this will determine the type of data and the way in which you store it (taken into account in the advisory report)
- Categorise the information to be used for data storage and monitoring, particularly in the area of 3R alternatives, and draw a distinction between those 3R alternatives that are still at a very early stage of development and those that are more highly developed (taken into account in the advisory report)

Improving the accessibility of data

Biomedical Primate Research Centre (BPRC)

- Try not to allow funding organisations (often those based outside the Netherlands) to impose additional obligations (e.g. that researchers should provide access to all of the crude data obtained from their animal procedures) (to be taken into account in partial advisory report 2)

Royal Netherlands Academy of Sciences (KNAW)

- Do not lose sight of the conflicting objectives between Reduction and Refinement (current policy seems to be opting for more animals with less individual distress/discomfort, rather than fewer animals with more individual distress/discomfort). If we focus only on the figures for the number of animals/animal procedures, this creates a false impression (taken into account in the advisory report)

Netherlands Association for Laboratory Animal Science (NVP)

- When planning the data storage system and monitoring systems, focus mainly on the numbers that have already been registered, use this to identify trends, and, if necessary, subject it to meta-analyses. Do not place any additional obligations on those working in the field (to be taken into account in partial advisory report 2)

Netherlands Federation of University Medical Centres (NFU)

- Do more in the area of data analysis and its interpretation. To this end, get more background information from those who are in a position to comment on its quality (taken into account in the advisory report)
- Compare trends, both at national and international level (taken into account in the advisory report)
- Be aware of the various assessment methods that will be used when trends are examined (to be taken into account in partial advisory report 2)
- Do not focus purely on quantitative data (numbers), also examine qualitative data (technological developments, strategic modifications) and use long-term analyses (e.g. five to ten years) to determine which developments in the area of 3R have or have not been successful (this is instructive in terms of assessing the impact of projects and the targeted use of funds for this purpose) (taken into account in the advisory report)
- Make it clear that a great deal of progress has been made, not only in terms of animal protection, but also in terms of the relative yields involved (taken into account in the advisory report)

Three Rs Alternatives Initiating Network (TRAIN)

- Bear in mind that trends and new developments that are important in terms of 3R development often take place outside the domain of laboratory animal use (taken into account in the advisory report)
- Approach experts from a range of different disciplines to gain a better understanding of the trends involved (taken into account in the advisory report)
- Get researchers or establishment licence holders to show exactly what savings they have achieved (animals, distress/discomfort, etc.) (taken into account in the advisory report)
- Information on 3R alternatives can be obtained from large international pharmaceutical companies under their Corporate Social Responsibility (CSR) policy or through their 3R officers. In addition, it helps if these companies are rewarded for their exemplary behaviour (taken into account in the advisory report)
- Create alertness among establishment licence holders, by asking them (via their Animal Welfare Body) for details of their efforts to implement 3R alternatives in relation to their overall efforts in terms of animal procedures. Bear in mind, however, that (as each licensed establishment will interpret the tasks of an Animal Welfare Body differently, i.e. there may or may not be a specific individual who has responsibility for the topic of 3R alternatives and the associated monitoring activities) some licensed establishments will have more difficulty with this than others (taken into account in the advisory report)
- Add value to the data storage system by combining prospective data (project applications) with retrospective data (welfare assessment, retrospective assessment, registration data) (taken into account in the advisory report)

Wil Research (on behalf of the industry)

- Include in the data storage system information on 3R methods that has not yet been included in guidelines, but which is being used in the early stages of the development of substances and drugs (taken into account in the advisory report)
- Ensure that, if they are invited to report about the savings achieved through replacement and reduction alternatives in regulatory research, establishment licence holders restrict themselves to citing the savings relative to the guidelines in force at that time (to be taken into account in partial advisory report 2)

Professional group of animal welfare officers

- Bear in mind that it is impossible for an internationally accessible database to cater both to public demand and to the needs of the scientific research community (taken into account in the advisory report)
- Get funding organisations, such as the Netherlands Organisation for Scientific Research (NWO), to require their researchers to save their raw data (not fully published, solid negative/neutral) and make it available, upon request (taken into account in the advisory report)
- Also, ensure that the Dutch research community saves and publishes data in the correct way, e.g. according to the ARRIVE Guidelines (taken into account in the advisory report)

HollandBio

- Input active data on developments such as Organ-on-a-Chip and Lab-on-a-Chip into the data storage system. Such data should have been published but not recorded as 3R (taken into account in the advisory report)

Other comments

Royal Netherlands Academy of Sciences (KNAW)

- Make it clear to the public at large that 3R development is not solely funded by money that has been earmarked for this purpose. Make it clear that the development and use of 3R alternatives (which are not always developed primarily as a 3R alternative but simply for the purpose of doing better research) are an intrinsic part of good practice in scientific research. It is very likely that the vast majority of the "3R alternatives" will be developed in this way, and that the researchers in question often do not even see them as 3R alternatives (taken into account in the advisory report)

Netherlands Association for Laboratory Animal Science (NVP)

- Describe state-of-the-art procedures in terms of best practices (not taken into account in the advisory report; codes of best practice are drawn up via other NCad activities)

Netherlands Federation of University Medical Centres (NFU)

- Keep in mind the fact that this aspiration can not lead to an increase in regulatory requirements for data provision or other activities. The European Directive prohibits the imposition of additional requirements relative to the regulations that were in place prior to 10 November 2010 and to Directive 2010/63/EU (taken into account in the advisory report and explored in further detail in partial advisory report 2)
- Re-examine the situation in five to ten years, to see how the challenge associated with the quality of recording and sharing data has developed in the field of clinical research involving human subjects, and learn from the experience gained there. This is up to date and many more resources have been allocated (at international level) (taken into account in the advisory report)

Wil Research (on behalf of the industry)

- Make every effort to ensure that this policy (and, with it, lines of research and research options) does not focus purely on figures and on reducing the number of animal procedures (taken into account in the advisory report)

HollandBio

- Encourage the further development of promising 3R alternatives (not taken into account in the advisory report)

Appendix 3: Summary of available data on laboratory animal use and 3R alternatives

A. Laboratory animal use

INPUT

Funding per type of establishment licence holder:

- Academic:
  - Direct funding: government (Ministry of Education, Culture and Science)
  - Indirect funding: funding organisations such as the Netherlands Organisation for Scientific Research (NWO), ZonMw, Royal Netherlands Academy of Sciences (KNAW), etc.
  - Contract funding: contract research and teaching, private funds (e.g. charities), targeted government grants, EU (e.g. Horizon2020 and IMI)
- Higher and secondary education:
  - Direct funding: government (Ministry of Education, Culture and Science)

- Indirect funding: funding organisations such as the Netherlands Organisation for Scientific Research (NWO), ZonMw, Royal Netherlands Academy of Sciences (KNAW), etc.
- Contract funding: contract research and teaching, private funds (e.g. charities), targeted government grants, EU (e.g. Horizon2020 and IMI)

- Public health and agriculture:
  - Direct funding: government (Ministry of Education, Culture and Science, Ministry of Economic Affairs, etc.)
  - Indirect funding: funding organisations such as the Netherlands Organisation for Scientific Research (NWO), ZonMw, Royal Netherlands Academy of Sciences (KNAW), etc.
  - Contract funding: contract research and teaching, private funds (e.g. charities), targeted government grants, EU (e.g. Horizon2020 and IMI)
- Industrial and contract research organisations (CRO)
  - Internal project funding
  - External project funding (with contract research)
- Breeding establishments:
  - Direct funding (academic, public health)
  - Industry and CRO
  - Any in-house research based on project funding

Data source for management and utilisation of data: In the case of all laboratory animal use for the purposes of research, teaching and breeding, once the IvD and DEC have made their recommendations, project licence applications are submitted to the CCD for review. Thus, the CCD is a potential central data source for planned laboratory animal use.

OUTPUT

Data sources for the management and utilisation of data per type of project output:

- Laboratory animal use: NVWA, establishment licensee (IvD), CCD
- Scientific publications: literature databases
- Theses: university libraries, individual scientific articles via literature databases
- Teaching: educational curricula
- Conferences and symposia: abstracts, proceedings, presentations

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Funding per type of establishment licence holder:

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- Higher and secondary education:
  - Direct funding: government (Ministry of Education, Culture and Science)
  - Indirect funding: funding organisations such as the Netherlands Organisation for Scientific Research (NWO), ZonMw, Royal Netherlands Academy of Sciences (KNAW), etc.

- Contract funding: contract research and teaching, private funds (e.g. charities), targeted government grants, EU (e.g. Horizon2020 and IMI)
- Public health and agriculture:
  - Direct funding: government (Ministry of Education, Culture and Science, Ministry of Economic Affairs, etc.)
  - Indirect funding: funding organisations such as the Netherlands Organisation for Scientific Research (NWO), ZonMw, Royal Netherlands Academy of Sciences (KNAW), etc.
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Appendix 4: Examples of 3R alternatives that are not cited/ recognised as such

Here are a few examples of 3R methods that were developed as spin-offs from academic research and that are widely used, but which were not cited as 3R methods:

- Optogenetics: non-invasively turning selected brain cells on and off by making these cells sensitive to light (using a virus that induces light-sensitive proteins in the cell). This makes it possible to temporarily influence the activity of nerve cells, which is a refinement relative to studies that explore the effects of permanent damage to the nervous system;
- Mini-transmitters: for the purpose of behavioural research on animals in the wild, researchers are currently using mini-transmitters that weigh just a few grams. After it has been fitted with one of these transmitters, an animal's location and movements can be monitored. Due to the smaller size and weight of this equipment, the animals' discomfort is also diminished. On the other hand, this technical development makes it possible to carry out this type of behavioural research on smaller animals. This can, potentially, increase the degree of welfare compromise involved in the use of smaller species

and in laboratory animal use;
- Vaccine production volume: each batch of vaccine needs to be tested for safety and efficacy. Batch volume has been increased, so fewer batches are required each year. This has led to a reduction in the number of animal tests.

Appendix 5: Available sources of information

A. The Netherlands Food and Consumer Product Safety Authority (NVWA)

The NVWA oversees compliance with the Dutch Experiments on Animals Act (Wod). It has the statutory duty of managing data on laboratory animal use in the Netherlands and of publishing this in the annual "Zo doende" reports. In addition to a report related to the Wod, a data report is submitted to the European Commission, in compliance with European legislation (2010/63/EU).

- Objective: accountability and information provision for policy, the political arena, and society on animal procedures and laboratory animals
- Nature of data: quantitative, retrospective information about animal procedures and laboratory animals (e.g. number of animals, number of animals bred, research objectives). Quantitative information, mainly relating to 3R alternatives for Reduction and Refinement (e.g. number of animals, severity classification, use of anaesthesia). Some establishment licensees voluntarily provide additional information about 3R activities
- Active since: 1978
- Scope of data: laboratory animal use by establishment licensees in the Netherlands, at procedure level

Options:

- Trends to be determined
- Facilitates the linking of searches for better focused monitoring
- Aspects of 3R policy established
- Existing activity can be fairly easily expanded by linking datasets and trend analyses
- Additional requirements for data to be reported can be added (possibly by means of legislative amendments)

Limitations:

- Changes in the (interpretations/definitions of) data to be reported lead to a break in the trend
- Differences in interpretation of data to be reported
- Adding supplementary requirements for data to be reported is over and above what is legally required and requires standardisation, additional work and central assessment of the input

B. The Central Authority for Scientific Procedures on Animals (CCD)

The CCD was established by the entry into force of the new Dutch Experiments on Animals Act (Wod, 18 December 2014). It is the Independent Administrative Body responsible for issuing licences for project applications that involve animal procedures for the purposes of teaching or research. The CCD manages prospective information on laboratory animal use and retrospective information (retrospective assessment) on primate research, research involving severe distress/discomfort, and any other specially designated projects. In addition, the CCD has a role in the accreditation of DECs and in yet to be determined project-transcending goals, such as data analysis with regard to applications.

- Objective: to inform the public about projects for which licences are granted;
- Nature of data: quantitative and qualitative prospective information about planned research projects involving laboratory animal use (e.g. number of project licences, objective of the project, species, number, estimated distress/discomfort). Qualitative information on 3R alternatives (3R development and application). Accessibly written descriptions of planned research projects involving laboratory animal use; the "non-technical summary" (NTS). Retrospective data on "retrospective analyses" of specific projects
- Active since: December 2014
- Scope of data: anticipated laboratory animal use in projects by establishment licensees in the Netherlands, at procedure and project level. Mandatory retrospective information on research involving severe distress/discomfort, and research involving non-human primates (retrospective assessment).

Options:

- Qualitative data on the options and limitations of 3R alternatives for specific research
- Quantitative data on projects in the Netherlands that involve animal procedures
- New database to be set up

Limitations:

- Data on planned research does not necessarily correspond to data on the actual number of animals used
- Political and societal pressure, as well as the need to qualify for funding, often cause scientific researchers to formulate unrealistically ambitious objectives for their research
- The database will only provide insights into trends from around 2020 onwards.
- The information provided about 3R alternatives, and especially about Replacement, will be in terms of the non-applicability of 3R methods to the specific objective of the project
- Animal procedures that have been replaced will not be visible to the database

C. Establishment licensees according to the Dutch Experiments on Animals Act (Wod)

Every establishment licensee in the Netherlands that uses, breeds or trades in laboratory animals is required (under the Wod) to set up an Animal Welfare Body (IvD) , which must be assigned various statutory duties. The establishment licence holder can serve as a source of information regarding the investments (in terms of time or money) made by the licensed establishment in 3R alternatives. The IvD's tasks include advising on animal welfare issues and on the application of the 3Rs. The IvD also supervises applications for project licences, as well as project implementation. In addition, depending on the licensed establishment involved, it may supervise the retrospective welfare assessment of the research project in question. The IvD manages information within the establishment licensee concerning every aspect of animal procedures, laboratory animals, animal procedure users and carers, and about 3R alternatives.

- Purpose: information for employees of establishment licensee (quality of scientific research), policy of establishment licence holder, conforms to legal requirement of Wod, registration data, laboratory animal use for the NVWA (laboratory animal science) annual report by establishment licensee.

- Nature of information: quantitative and qualitative information on laboratory animal use (e.g. the classification per objective of the research, credentials and competence of researchers and other personnel involved, refinement and trends in laboratory animal use) and qualitative information on the development and implementation of 3R alternatives.
- Active since: establishment licensees have reported to the NVWA since 1978. The IvDs have been active since 2014.
- Scope of information: animal procedures, laboratory animals, and 3R alternatives used within the licensed establishment to which the relevant IvD associated, at project level, and per procedure.

Options:

- As part of its statutory duties, due to its involvement in applications for project licences and in the working protocol (and, often, in the institution's annual laboratory animal science report), IvD has an understanding of the development and implementation of 3R alternatives within the institution, particularly in terms of Reduction and Refinement
- The IvD signals the replacement of an animal procedure by in vitro methods (or other 3R methods)
- The IvD has insight (at an early stage) into developments in laboratory animal use

Limitations:

- There is, as yet, no structured and centralised database of IvD data
- The work of various IvDs has not yet been standardised, resulting in a diversity of methods and themes
- 3R alternatives that only indirectly affect laboratory animal use may not be visible to the IvD
- Requisite harmonisation and documentation of data storage
- Reporting on 3R development and implementation is not part of the IvD's statutory remit

D. Funding organisations

Biomedical research projects and other research projects that may involve animal procedures and 3R developments (e.g. in vitro research) are funded by a wide range of funding organisations. This involves public (direct or indirect funding, such as NWO, ZonMw and Horizon2020) or private funding (contract funding, such as patient associations, charities and industry).

There are only a limited number of funds that specifically target the development and validation of 3R methods. In the Netherlands, ZonMw manages the More Knowledge with Fewer Animals (MKMD) programme, which is a continuation of previous programmes by the Platform for Alternatives to Animal Testing (PAD), ZonMw's Limits for Animal Procedures I, II and III, and ASAT (Assuring Safety without Animal Testing). In addition, the Ministry of Economic Affairs and the animal welfare organisation StichtingProefdiervrij fund (via ZonMw) 3R research, and a number of licensed establishments, including those in the industry, support specific 3R projects. The ProjectNet programme is used by ZonMw-funded researchers to register progress reports and final reports for the organisation's projects. This is not the case for projects funded from other sources, or there is still a lack of potentially relevant indicators.

At international level, 3R research is funded by the European Commission's Horizon2020 programme (formerly known as the Framework Programmes). Within individual EU Member States it is supported by publicly funded programmes (e.g. NC3Rs in the UK) and private organisations (e.g. the Doerenkamp Zbinden Foundation in Germany).

- Objective: (if available) the provision of information about the allocation of specific funds.
- Nature of information: qualitative information (e.g. description of projects, research information, possible application, impact) on approved projects involving animal procedures, 3R alternatives, or both
- Active since: dependent on grant provider
- Scope of information: Varies greatly between funding organisations, as it is related to the objectives of the organisation in question. 3R alternatives, developing new models

Options:

- Data is available on projects in which 3R alternatives are used or developed, and where funding is not primarily focused on the 3Rs
- The impact and output of projects can be monitored over time

Limitations:

- Agreements on patenting, intellectual property and confidentiality can curb openness about impact and output
- Sources are diverse in nature, with both national and international distributions; this makes it difficult to set up a uniform strategy for the collection of data
- Collected data is limited to grant-funded research

E. Literature databases

The results of animal experimentation and 3R alternatives are recorded in scientific publications (e.g. articles, theses, reports, books and annual reports). It is certainly the case for scientific articles and theses that the information they contain is stored in international databases like PubMed , Medline and Web of Science , and, where relevant, also in specific databases like those that have been created for 3R alternatives (see sub-section 4.6). These files are digital and can be searched using full-text queries, because classification systems are indexed. For the 3Rs, specific "3R alternatives search criteria" are available, via SYRCLE , for example. However, their usefulness is limited to research that is carried out for the express purpose of 3R. The search results also need to be extensively checked for the correct interpretation of terminology. Information can provide both quantitative data (number of publications on an in vitro model, citations, impact factor) and qualitative data (developments in specific academic disciplines).

- Objective: consolidating scientific literature and making it available, recording research results
- Nature of information: quantitative (e.g. number of publications on specific models, number of citations, researchers) and qualitative information (trends in development), data research projects and procedures, scientific project level
- Active since: dependent on literature database, generally decades
- Scope of information: Scientific publications, scope depends on literature database and search engine involved

Options:

- Data from published literature can be obtained through the use of synthesis of evidence with search engines and topic-specific search criteria. Experts can signal non-recognised 3R methods and 3R research that is not associated with the laboratory animal area.
- Insight into policy impacts involving innovative techniques (and associated trends over the years) can be gained by comparing publications from Dutch establishment licensees against the total number of publications on these techniques
- Meta-analyses of specific topics can be used to derive details of developments and trends, and to implement a policy that is focused on these same topics

Limitations:

- The details of some animal experimentation or 3R research remain unpublished, and so are not available in literature databases. This includes research carried out in industry, as well as some solid negative/neutral data from animal experimentation
- Simple search criteria generate a relatively large amount of noise, as 3R terms like Replacement and Reduction are seldom referred to in this way in publications
- In many articles, the replacement of laboratory animals is just a by-product of research in which the key issue was the development of an innovative technique purely for scientific or cost-related purposes

F. 3R websites

There are both national and international websites that manage information about 3R alternatives. Some address specific topics (e.g. the "Interspecies website" and the "Humane endpoints website" that are made available via the 3R platform of Utrecht Life Sciences) while other sites cover the full range of 3R alternatives.
One example is the Norecopa platform, which includes a "3R Guide " to provide access to information on a selection of guidelines, background information on in vitro models (including textbooks), 3R approaches and links to other websites; however it does not permit the monitoring of 3R developments within primary studies. The Go3Rs Search Engine can indeed be used to monitor primary studies but, for the time being, this database focuses primarily on toxicological research. Other websites also offer the option of "3R searches", such as CCAC's Three Rs Searches & Animals Index , the CAAT Media Center , ECVAM's 3R Search Guide , or the Resources page of the NC3Rs website .

- Objective: to facilitate literature reviews, overviews of available 3R models, organisation, links to relevant organisations
- Nature of information: qualitative and quantitative information (e.g. insight into existing 3R models, status of models, literature reviews and activities such as conferences and workshops) sometimes focused purely on a specific field of research, sometimes wider in scope.
- Active since: dependent on website in question
- Scope of information: the scope of 3R alternatives (e.g. policy, research, application, impact) ranges from very wide-ranging (e.g. NORECOPA) to more limited options with a specific focus

Options:

- Websites can be made accessible in a structured way, e.g. by creating categories for research, including links to relevant websites

Limitations:

- Because of the wide variety of information involved, it is not possible to centralise this information

G. Beoordelingsautoriteiten

Some animal procedures are carried out to conform to regulatory requirements, as in the case of the registration of a new drug, obtaining market approval for a chemical, or the release of a batch of vaccine. In the Netherlands, responsibility for this lays with various assessment authorities, such as the Medicines Evaluation Board (MEB) , or the Board for the Authorisation of Plant Protection Products and Biocides (CTGB) . Demands on the various specific areas of safety studies and efficacy studies are documented in a variety of national, European or international testing provisions.

- Objective of information: to highlight regulatory developments both with regard to additional regulatory guidelines for animal tests (with respect to registration or the release of substances/products that are subject to legal requirements) as well as the acceptance of 3R alternatives
- Nature of information: quantitative and qualitative information. Test guidelines specifying numbers of animals, procedure, endpoints, distress/discomfort. There is also information on test guidelines, based on 3R alternatives. Also, information about ongoing 3R research and possible validation studies
- Active since: dependent on assessment authority
- Scope of information: dependent on regulatory institution: OECD (toxicity), EFSA (food), EMA (drugs and biologicals), European Pharmacopoeia (release tests drugs/vaccines), national assessment authorities like the CBG for the registration of drugs or the CTGB for the registration of plant protection products and biocides. Legally regulated research, validated and accepted 3R methods.

Options:

- Test guidelines are subject to the condition that central monitoring is possible. The RIVM plays a central role in setting up a network of regulators.

Limitations:

- Limited access of data in registration procedures, due to considerations of confidentiality

The Ministry of Economic Affairs has instructed the RIVM to organise and structure Dutch coordination efforts in the area of promoting the validation, regulatory acceptance and implementation of 3R methods for determining the safety and/or efficacy of chemicals, drugs and vaccines. In that context, the RIVM is currently establishing a national knowledge network in the area of regulatory research (and the associated 3R developments). This network could serve as a valuable source of information.

Footnote

1 Dutch Experiments on Animal Act Article 14c.1. The Animal Welfare Body performs the following tasks: d) monitors the development and results of projects, taking into account the impact on the animals used, identifies elements that can also contribute to Replacement, Reduction and Refinement, and advises on this matter. http://wetten.overheid.nl/BWBR0003081/

2 "Not all that counts can be counted, and not everything that can be counted counts". (Albert Einstein)

3 http://www.rijksoverheid.nl/documenten-en-publicaties/kamerstukken/2014/02/28/plan-van-aanpak-dierproeven-en-alternatieven.html

4 "Open Data" refers to datasets that are made available under an open licence, thus permitting unrestricted access and reuse. The conditions under which such data are made available are described in licences and terms and conditions of use. In the Dutch National Data portal, the Ministry of the Interior and Kingdom Relations uses the following criteria for open data: Open Data is public; it is not subject to any copyright or other third party rights; the data in question has been funded from public resources made available for the purpose; the data preferably conform to "open standards" (no barriers to its use by IT users or IT providers); Open Data is preferably computer-readable, to enable search engines to locate information in documents. https://data.overheid.nl/

5 'Open Data' zijn datasets die met een open licentie beschikbaar worden gesteld zodat toegang en hergebruik zonder beperkingen mogelijk is. De voorwaarden waaronder de data beschikbaar zijn, worden beschreven in licenties en gebruiksvoorwaarden. Het ministerie van Binnenlandse Zaken hanteert in het Nationale Dataportaal de volgende criteria voor open data: Open Data zijn openbaar; er berust geen auteursrecht of andere rechten van derden op; de data zijn bekostigd uit publieke middelen, beschikbaar gesteld voor de uitvoering van die taak; de data voldoen bij voorkeur aan 'open standaarden' (geen barrières voor het gebruik door ICT-gebruikers of door ICT-aanbieders);Open Data is bij voorkeur computer-leesbaar, zodat zoekmachines informatie in documenten kunnen vinden. https://data.overheid.nl/

6 In the advisory report that the NCad is to issue in 2015, about "synthesis of evidence" and "systematic reviews" in animal procedures, synthesis of evidence is defined as the process of synthesising relevant literature to arrive at scientifically well informed, accessible summaries of the available evidence. In the synthesis of the relevant literature and available materials, there is a choice of a number of forms, including narrative reviews, systematic reviews, databases and expert panels.

7 Dutch Experiments on Animal Act Article 14c.1. The Animal Welfare Body performs the following tasks: d) monitors the development and results of projects, taking into account the impact on the animals used, identifies elements that can also contribute to Replacement, Reduction and Refinement, and advises on this matter.http://wetten.overheid.nl/BWBR0003081/

8 Animal Experiments Openness Code: https://www.knaw.nl/nl/actueel/publicaties/code-openheid-dierproeven

9 https://data.overheid.nl/

10 https://ec.europa.eu/dgs/connect/en/content/data-value-chain-european-strategy

11 The advisory report on synthesis of evidence and systematic reviews in animal procedures that the NCad expects to issue at the end of 2015 explores in further detail the options and limitations of using these methods in this area

12 Intellectual property

13 Dutch Experiments on Animal Act Article 15: "Breeders, suppliers and users are required to keep records concerning the breeding, acquisition, delivery, release or release for rehoming, keeping, and sacrificing animals and concerning projects in which animals are used and to submit data to Our Minister, all in accordance with, or pursuant to, an order in council which is imposed in that regard. In accordance with or pursuant to the order in council further topics can be designated, records should be kept in this regard. http://wetten.overheid.nl/BWBR0003081/

14 http://www.bfr.bund.de/en/zebet-58194.html

15 http://www.ccac.ca/en_/

16 http://www.nc3rs.org.uk/

17 https://www.gov.uk/government/organisations/home-office

18 http://www.foedevarestyrelsen.dk/fvst_ansvar_opgaver/Sider/Dyreforsoegstilsynet.aspx

19 https://www.gov.uk/government/publications/working-to-reduce-the-use-of-animals-in-research-delivery-plan

20 NC3Rs: The Medical Research Council's National Centre for Replacement, Refinement and Reduction of Animals in Research (NC3Rs). Evaluating Progress in the 3Rs: The NC3Rs Framework.

Procedure

In preparing its advisory reports, the NCad makes use of the services of experts from the Netherlands and elsewhere. Stakeholders and chain partners are also consulted.

In the course of preparing this advisory report, the following experts were consulted:
Barbara Grune (ZEBET Germany), Gilly Griffin (CCAC Canada), Judy MacArthur Clark (Home Office, United Kingdom), Mark Prescott (NC3Rs United Kingdom), Peter Bollen (member 'Dyreforsøgstilsynet', University of Southern Denmark), Pascalle van Loo (Animal Welfare Body of the Netherlands Organisation for Applied Scientific Research), Pieter Verbost (Animal Welfare Body of the Radboud University Medical Center), Willem Kamphuis (Animal Welfare Body of the Royal Netherlands Academy of Sciences), Erica van Oort (Netherlands Organisation for Health Research and Development), Noortje Reeuwijk (Netherlands Food and Consumer Product Safety Authority), Jeroen Peijs (Netherlands Food and Consumer Product Safety Authority), members of the Central Authority for Scientific Procedures on Animals, Anne Kienhuis (National Institute of Public Health and the Environment), Merel Ritskes-Hoitinga (Systematic Review Centre for Laboratory animal Experimentation), Marlies Leenaars (Systematic Review Centre for Laboratory animal Experimentation).

In the context of the societal expert group on animal procedures and alternatives (MEDA), the representatives of the following community groups (who are all experts in the relevant fields) also contributed to this advisory report: Biomedical Primate Research Centre (BPRC), Royal Netherlands Academy of Sciences (KNAW), Netherlands Association of Animal Ethics Committees (NVDEC), Dutch Association for Laboratory Animal Science (NVP), Netherlands Federation of University Medical Centres (NFU), Three Rs Alternatives Initiating Network (TRAIN), Wil Research (on behalf of the industry), the professional group of animal welfare officers, and HollandBio.

Due to personal circumstances, one of the members of the NCad was neither able to take part in the final discussions nor in completing the advisory report. There is full consensus among the remaining members with regard to the content of the advisory report.

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The Netherlands National Committee for the protection of animals used for scientific purposes (NCad) was appointed for the protection of animals used for scientific purposes and for education. The NCad achieves visible improvements that are specifically related to the Replacement, Reduction and Refinement (3Rs) of animal procedures and to the associated ethical review in scientific research (including applied scientific research) and teaching. Its goal, in doing so, is to minimize laboratory animal use at both national and international level.