

# *Indicators, management and utilisation of data for monitoring laboratory animal use and 3R alternatives, part 2*

Opinion of the Netherlands National Committee for the protection of animals used for scientific purposes (NCad)  
commissioned by the Minister of Agriculture



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



## The NCad and its methods

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

## Members of NCad

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## Summary

In a letter dated 31 March 2015 the Minister for Agriculture requested the Netherlands National Committee for the protection of animals used for scientific purposes (NCad) to issue an opinion on indicators, management and utilisation of data for monitoring laboratory animal use and 3R alternatives. NCad was asked to publish its opinion in two parts. The first part was published in November 2015. Part 1 focused on the management and utilisation of data on laboratory animal use and 3R alternatives. NCad has advised the disclosure of data concerning laboratory animal use and the 3R alternatives. Via a new centralised data warehouse – a virtual network of many stakeholders – all information concerning animal procedures and 3R alternatives that is available to the government – should be made accessible as open data.

This advisory report (Part 2) meets the second part of the request and identifies indicators that could contribute to a better understanding of issues surrounding the use of laboratory animals and 3R alternatives, and developments in these fields. These can be used for the development and implementation of policy. The guiding principle of both parts of the advice is the aspiration of the Minister as formulated in the Action Plan for Animal Procedures and Alternatives to promote animal welfare and to minimise laboratory animal use as much as possible.

With regard to the identification of indicators, NCad advises the Minister for Agriculture as follows:

The design of a centralised data warehouse should be based on two goals:

- 1) the collating of data on laboratory animal use and 3R developments for further analysis of trends and otherwise, using monitoring indicators
- 2) the further disclosure of knowledge to the research community, the public, and the government.

The centralised data warehouse should be built up in stages, whereby the government should take the initiative during the first stage, which is focused primarily on achieving the first goal. A development period of two years is estimated for this phase. The second phase, focused principally on the second goal, involves continuing activities that require more preparation time and that can be developed in a more organic way by leaders in the research community, commissioned by the government.

The indicators selected by NCad together provide a clear and broad picture of developments in laboratory animal use and 3R activities. The hard, quantitative monitoring indicators in particular are focused on registration data from the Netherlands Food and Consumer Product Safety Authority (NVWA) and the Central Authority for Scientific Procedures on Animals (CCD). The evaluation indicators are semi-quantitative or qualitative in nature and especially suitable for making trend analyses and forming anticipated developments and other evaluations.

A 3R monitor should be set up to measure the extent to which within the licensed establishments attention is focused on laboratory animal and 3R policy. In addition, having regard to the need to safeguard privacy and market position, the research community should be encouraged to follow the policy of active public disclosure, especially with regard to relevant information on the application of the 3Rs.

A central body should be given the task, by means of a strict regime and a process-driven approach, to ensure the layout of the data warehouse, focused on the disclosure of data and the ease of searching for data. A party should be chosen that, without having a direct interest, can also subsequently be made responsible for drawing up trend analyses and evaluations, and which enjoys the confidence of the research community. NCad would suggest National Institute for Public Health (RIVM) for such a role or a suitable academic establishment.

NCad envisages that the first goal of the data warehouse can be realised with an investment of a few hundred thousand euros. Structural management costs are estimated at between two and three hundred thousand euros per year. The cost of the second goal will depend heavily on the level of ambition and the willingness of the research community to contribute, either by making data available or otherwise. To get the required action underway, NCad believes that it is desirable that the government should make an annual budget available of at least half a million euros over the coming years.

These amounts are well-informed estimates based on interviews with experts. In the first phase of the allocation of the project to the implementing organisation, a more definitive budget needs to be drawn up on the basis of more thorough preliminary research.

### **Keywords**

Monitoring, open data, transparency, centralised data storage system, 3R, laboratory animal use, data warehouse, indicators

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# 1. Introduction

More openness and transparency about animal procedures and the possibilities of replacing, reducing and refining them (3Rs) are essential to prudent laboratory animal use and the optimal availability of scientific information. For this reason, Netherlands National Committee for the protection of animals used for scientific purposes (NCad) recommended the disclosure of data on the use of laboratory animals and the possibilities of the 3Rs to the Minister for Agriculture in October 2015. For this purpose, NCad envisaged the creation of a data warehouse in which all information on animal procedures and 3Rs that is available to the government is made accessible as open data.

Data on laboratory animal use and the 3Rs is still insufficiently available and there is a particular lack of insight into developments and relationships. As a result of this, the picture that policymakers, researchers and the public have of this topic is often incomplete. Misunderstandings easily arise because discussions are held on the basis of inaccurate assumptions. Opportunities can also be missed because prior experiences cannot be adequately used. Making the data on laboratory animal use and the 3R alternatives available as open data in a data warehouse would make it possible to combine and analyse data from different sources. It would therefore increase the accessibility of data for policymakers, scientists and research journalists, for example, and enhance insight into developments in the area of laboratory animal use and the 3Rs.

NCad recommended to the Minister to follow the government's open data policy and disclose all information on laboratory animal use, animal procedures and 3R alternatives that is available to the government, insofar as this may be disclosed taking account of the sensitivity of privacy issues and the protection of intellectual property. This advice and existing practice in the Netherlands go further than is currently the case in Europe. For this reason, NCad recommended that the Minister take the lead and also make efforts towards a European open data policy.

The data can be further enriched by the focused and systematic collation of data on laboratory animal use and the development and application of 3R alternatives. NCad recommended adapting the annual reporting on animal procedures and laboratory animals so that accessible and explanatory insight can be provided into trends in the area of animal procedures and 3R activities, as well as their impact on laboratory animal use. This requires the designation of one or more parties that are responsible for an integrated report.

This follow-up advisory report (Part 2) details indicators and criteria that can be used to form a better picture of the developments in laboratory animal use and the 3Rs. It also explains how this can be further implemented and estimates the costs and benefits associated with the establishment of a data warehouse.

## 2. Request for opinion

In her letter of 31 March 2015, the Minister for Agriculture requested NCad, taking account of available national and international opinions and studies, to give its opinion on the management and utilisation of data on laboratory animal use and 3R alternatives, as well as to identify indicators that could contribute towards a better understanding of developments in relation to laboratory animal use and 3R alternatives.

NCad was requested to pay attention in its opinion to the following aspects relating to developments in the area of laboratory animal use and 3R alternatives:

- Making better use of available data, and improving its accessibility
- Listing any gaps
- Identifying indicators;
- Listing and prioritising the main short 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.

NCad was asked to divide its advisory report into two parts:

1. management and utilisation of data on laboratory animal use and 3R alternatives, in respect of which NCad issued the advisory report ‘Indicators, management, and utilisation of data for monitoring laboratory animal use and 3R alternatives, Part 1’;

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.

## 3. Advisory report

In the advisory report ‘Indicators, management, and utilisation of data for monitoring laboratory animal use and 3R alternatives, Part 1’, NCad outlined the concept and potential significance of a data warehouse, in which data on laboratory animal use and 3R developments are to be stored and made publicly available. After all, for a broadly-supported Dutch laboratory animal policy, in which the 3Rs are the key element, it is important to gain insight into developments concerning both laboratory animal use and the 3R alternatives. Appendix I summarises the recommendations from Part 1 of the advisory report.

For the purpose of drawing up this advisory report, discussions have been held with representatives of relevant organisations. Representatives of community groups, including the Societal Expert Group on Animal Procedures and Alternatives (MEDA), have also given their input. Appendix 2 contains the vision of each of the consulted community groups on this topic.

In this Part 2 of the advisory report, NCad delves deeper into the detail of the first part in order to be able to further substantiate its feasibility and focus on data storage. An important topic is determining the indicators and accompanying parameters for monitoring developments in laboratory animal use and 3R alternatives. The purpose of these indicators serves as the starting point in this regard. It is not possible to translate everything into indicators and not all possible indicators are equally relevant.

NCad has arrived at the following recommendations and suggestions.

1. NCad recommends that the Minister bases the design of the data warehouse on two goals:
  - a. The collation of information on laboratory animal use and 3R developments for further trend analyses, using monitoring indicators;
  - b. The further disclosure of knowledge to the research community, the public and the government.
2. NCad recommends building the data warehouse in stages. The first stage must focus mainly, but not exclusively, on the first goal. The government, in particular, must take the initiative for the first part. The second part can be developed in a more organic way by leaders in the research community, with incentives for this purpose from the government. NCad is prepared to function as a sounding board, particularly during the start-up phase. A two-year development period is expected to be a reasonable estimate for the first part. The second part will be a continual activity that also requires more preparation time.
3. NCad recommends initially using a limited number of quantitative and qualitative indicators, as detailed in Appendix 2 to this advisory report. These indicators are selected such that they provide a representative and broad picture of developments in laboratory animal use and 3R activities. The hard, quantitative monitoring indicators focus particularly on registration data from the NVWA and CCD. The other indicators are semi-quantitative or qualitative and are especially suitable for making trend analyses and forming future expectations and other evaluations.
4. NCad recommends the development and set-up of a 3R monitor. This qualitative monitoring, which is to be carried out in the field and, as regards its design, is comparable to a customer or employee satisfaction survey, measures whether and to what degree attention is actually paid within the institutions to laboratory animal and 3R policy.
5. Much of the relevant information about the application of the 3Rs is not currently made public. NCad sees a major advantage for the research community in sharing this knowledge via open data. Having regard to the protection of privacy and market position, it recommends following the policy of active disclosure (open data) here.
6. From NCad's perspective, the data warehouse is not a physical place for the central storage of all data, but rather a virtual network of many stakeholders involved. A central unit, as yet to be named, will be tasked by the Minister to attend to the design, standardisation of terminology and technical links. The core task in this regard is the disclosure of data and making it searchable.

7. The establishment of a data warehouse requires a strict regime and process-based approach to obtain a pledge and commitment from the parties involved and lay a firm foundation for future development with leaders from the research community. For this reason, a party that can also be responsible later for drawing up trend analyses and evaluations, without holding any direct interest itself, and which enjoys the confidence of the research community, should be chosen to manage the data warehouse. Due to RIVM's role as the scientific adviser to the government, NCad believes that it would be an appropriate party to put this advisory report further into practice, although suitable academic institutions can also be considered for this purpose.
8. NCad expects that the first goal of the data warehouse can be achieved by investing a few hundred thousand euros. Structural management costs are estimated at between two and three hundred thousand euros a year. The costs of the second goal are more difficult to estimate because these depend heavily on the level of ambition and the willingness of the research community to contribute by making data available or otherwise. In order to set the desired wheels in motion, NCad believes it would be advisable for the government to budget at least half a million euros a year over the coming years. This amount is a well-informed estimate based on interviews, which NCad notes does not take account of any strokes of luck or setbacks, such as making source data technically suitable for inclusion in the data warehouse. A more definitive budget can be drawn up only once more thorough preliminary research is conducted in the first phase of the allocation of the project to the implementing organisation.

NCad is convinced that following the above recommendations will result in a far stronger basis for the public debate on the desired developments in laboratory animal use. The existing knowledge of 3R activities and applications can also be far better disclosed for science, policy and society.

## 4. Substantiation of the advisory report

The substantiation of this advisory report focuses firstly on the 'what', followed by the 'how'. A distinction is also made between the two goals that are served by the data warehouse, namely:

- a. The collation of information on laboratory animal use and 3R developments for further trend analyses, using monitoring indicators;
- b. The further disclosure of knowledge and information to the research community, the public and the government.

### 4.1 Indicators for monitoring developments in laboratory animal use and 3R alternatives

Through monitoring, insight is gained into developments in animal laboratory use and 3R alternatives in the Netherlands. Monitoring can be defined as the systematic and periodic observation and presentation of developments that are deemed relevant to policy.

The primary goal of monitoring is to enhance the understanding of developments, trends and policy effects.

'Zo doende', published by the NVWA each year, is an important source document for monitoring, particularly as regards laboratory animal use, but also in the area of 3R activities. However, due to the choices in themes and manner of reporting, there is only a limited opportunity to make connections between the data, both within one year and among the years. By linking data from various data sources and making use of specific monitoring indicators, developments and trends can be made visible and subsequently evaluated. Identified developments can give rise to the coordination or alteration of policy, after which the effects of this become clear through evaluation indicators.

If the source data, which is already available to the government, is made available as open data, this also becomes useful to third parties for evaluation and analysis. This extends insight, especially if this information is combined with information from other sources.

#### **4.1.1. Purpose of the indicators**

Indicators shed light on developments and trends in laboratory animal use and 3R alternatives. The emphasis in the current political debate lies mainly on quantitative data: the number of animals (in experiments, in education, being bred, and killed in stock), developed 3R alternatives, etc. In order to intensify and balance the debate, it is necessary for these numbers to be specified further, by means of qualitative information and evaluation:

- more insight into the expected and actual returns on laboratory animal research (the benefits, focusing on more knowledge with fewer animals);
- more insight into the actual effects of the 3R policy (e.g. less distress and better laboratory animal welfare);
- insight into the efforts relating to 3R alternatives;
- insight into trends and future expectations (when and where 3R alternatives can be applied).

Indicators create opportunities for policy-based adjustments when these are deemed necessary, for example because of wide social debate. A broader raft of indicators can also avoid an overly one-sided focus on only the number of animals. The use of more animals does not necessarily have to be unfavourable, provided this is compensated for by a significant health gain and the welfare interests of individual animals are taken explicitly into account. The challenge lies in generating increasingly more reliable knowledge with animal-free methods, fewer laboratory animals and/or less distress.

Although the reality will always be more complicated, the indicators must serve as a type of policy dashboard. These can then be looked at in more depth in order to further define developments and trends.

For the sake of clarity, NCad recommends that the Minister starts by using a limited set of indicators for monitoring developments in laboratory animal use and 3R alternatives, using as much of the data that is already available to the government, in principle.

By means of periodic monitoring on the basis of this set of monitoring indicators, developments in relation to prior measurements can be properly identified. Additional evaluation indicators can be used for further evaluation.

#### **4.1.2. Possible indicators and their significance**

Laboratory animal use and 3R alternatives will be monitored on the basis of quantitative and qualitative data, existing and newly collated data, and on various levels. The substantive examination will include laboratory animal use, for example by animal species and research objective, as well as the percentage of ‘animals killed in stock’ and distress. Much of this information is available from current sources or sources under development, particularly at the NVWA and CCD. This mainly involves quantitative information.

It is more difficult to gain insight into developments in the area of 3R alternatives. After all, these are not always visible in licensing and registration, especially if replacement alternatives that are developed and applied outside the area of animal procedures are involved. A more qualitative approach will be needed in order to gain this insight, such as additional studies into developments and activities, workshops and consultation of trade associations.

The need for a more qualitative approach in order to gain insight also applies to how the implementation of the 3Rs is dealt with in project licence applications. This is carefully assessed by the Animal Welfare Body (IvD), the Animal Ethics Committee (DEC) and the CCD.

Nonetheless, is it insufficiently clear whether there is a culture among researchers and licensed institutions in which alternatives to animal models are already explored in an early stage, when the research question is formulated.

For this reason, NCad recommends gaining insight into the climate in which laboratory animal use occurs and the scope (opportunities and obstacles) that exists in that for 3R developments and applications, at the level of daily practice, ‘in the workplace’, by questioning those involved in animal procedures and experts. This should be done every two years by means of a professionally designed 3R monitor.

In order to measure the success of the policy, it is not only important to understand performances in the research community, but also the contributions that the institutions involved make in that regard. For example, what are the effects of evaluation by the CCD, the enforcement policy of the NVWA, and what is the impact of advisory reports and Codes of Practice published by NCad? Although it is perhaps still premature at this stage, NCad recommends that performance indicators for these institutes should be included in the data warehouse structure. Questions about this can possibly be included in the 3R monitor.

The monitoring choice that incorporates substantive, cultural and process-based facets (triangulation) stems from the observation of laboratory animal use and 3Rs as a broad, varied and multidisciplinary field. Looking only at one aspect does not suffice. In this way,

quantitative and measurable results can be identified and substantiated with qualitative monitoring outcomes.

NCad applies the following criteria in the choice of indicators for monitoring and evaluating laboratory animal use and 3R developments:

- in harmony with European registration requirements;
- positively orientated (i.e. ‘what has been done?’ and not ‘what is missing?’);
- practical to use and implement (thus relatively simple and modest in design);
- based on information that can be verified in any way.

Because criteria and indicators can differ in nature and relevance for each research domain, NCad also recommends adopting and evaluating these for each domain or sub-domain. Perhaps the most useful classification for this purpose<sup>2</sup> is to distinguish among fundamental research, applied research and regulated research. These domains can be subdivided further into several sub-domains according to need.

As policy-based, relevant monitoring indicators, NCad recommends:

1. **Animals used in animal procedures:** NVWA data on the number of animals used, for which research objective, and with which degree of distress, etc. is used for this purpose.
2. **Animals killed in stock:** NVWA data on the number of animals that are killed in stock, the number of genetically modified animals, the animal species involved, reasons why animals are killed in stock, etc. is used for this purpose.
3. **Anticipated laboratory animal use:** CCD data on the planned number of animals needed for approved project licensing applications, for which research objective, and with which degree of distress, etc. is used for this purpose.
4. **3R culture within licensed institutions:** data from the new systematic and periodically repeated survey that is to be created, the 3R monitor, is to be used for this purpose. Employees and others involved in animal procedures are to be questioned on the culture and efforts within their own institution with regard to 3Rs, the laboratory animal and 3R policy, the impact and possibilities thereof, etc.

This dashboard of four monitoring indicators already gives some insight into laboratory animal use and 3R alternatives. This can be broadened and deepened by supplementing the dashboard with indicators that have more of an evaluative approach, the evaluation indicators.

- a. **'Anticipated laboratory animal use' – 'animals used in animal procedures'**: by combining monitoring indicators 3 and 1, insight is gained into the relationship between anticipated laboratory animal use and the actual animals used in animal procedures, including how this developed over the years.
- b. **'Animals killed in stock' – 'animals used in animal procedures'**: by combining monitoring indicators 2 and 1, insight is gained into the relationship between animals used in animal procedures and animals that are killed in stock, including how this has developed over the years.
- c. **'Anticipated degree of distress' – 'actual degree of distress in animals used in animal procedures'**: by combining monitoring indicators 3 and 1, specifically the parameters relating to the degree of distress, insight is gained into the relationship between the anticipated and the actual degree of distress, including how this has developed over the years.
- d. **Performance indicator for promising developments in 3R alternatives**: in targeted studies, and for each research domain, for example, a performance indicator of the promising breakthrough technologies with 3R impact is generated on the basis of scientific publications, expert consultations and opinions (such as from trade associations).
- e. **Performance indicator for the financing of 3R alternatives**: according to a methodology to be developed with financiers, such as the Netherlands Organisation for Health Research and Development (ZonMw), a performance indicator of earmarked 3R budgets and their impact is generated.
- f. **Performance indicator for the implementation of 3R alternatives**: in targeted studies, a performance index of the implementation of 3R alternatives is periodically generated, for each research domain, on the basis of expert panels and data from IvDs, ZonMw, the European Centre for the Validation of Alternative Methods (ECVAM) and RIVM.
- g. **Perspective index for each animal species and area of application**: in targeted studies, a perspective index of the anticipated direction of 3R development and the anticipated rate is periodically generated, for each animal species and area of application, on the basis of expert panels.
- h. **Performance index for the effect of policy and investment**: a methodology can be designed in conjunction with the research community to show the resources used by licensed institutions (FTEs and financial) for animal procedures and 3R research, as well as their output and impact, in a performance index. The data from the 3R monitor, as possibly expanded, can be used for this purpose. Scientific publications, reports and progress briefings are also used for the output of the above investments and efforts. The impact of the above investments in and efforts towards animal procedures and 3R research can be expressed in practical applications and/or focused follow-up

studies. NCad is aware of the additional workload that the required information implies for all licensed institutions, but also realises that this will give rise to a powerful instrument by which institutions that excel in the area of the 3Rs can positively set themselves apart. Similar earlier initiatives, including in the area of sustainability (annual environmental report) and Access to Medicines (ATM) have proved very successful, both as regards their objectives and their positive image and familiarity in society. The specification and implementation of such an index requires effort and very meticulous and structural involvement of an independent and reliable party.

well-served by an accessible database that can be consulted during the preparation of research and in respect of which evaluations can be performed.

This also involves information that is usually not published or is not obviously available, but known to the licensed institutions, the IvDs, Animal Experiment Committees (DECs), CCD, NVWA, grant institutions and literature sources. This information often goes somewhat deeper than is registered. Some of this data, when combined with other data, is ideally suited to providing insight into laboratory animal use and 3R alternatives.

An example of this is the information on 3Rs in project licence applications. As a rule, this is discussed at depth with the IvD, described in the project licence application and concisely set out in the Non-Technical Summary (NTS). Apart from the NTS, further information is not currently available to other researchers. In striving towards sharing information on this point and the principle of open data, NCad finds that this information must be public, in principle, within preconditions for the protection of privacy and market position.

Other data of licensed institutions on laboratory animal use, animal procedures and 3R alternatives, which could be of importance to other researchers or laboratory animal scientists, would be able to be actively shared via the data warehouse. In this way, knowledge is not only shared, but a better view of developments also arises. An analysis of the number of animal studies in which the research objective is achieved can, for example, provide insight into the value of animal

The indicators are detailed further in Appendix 2, with an explanation of what an increase or decrease in these indicators (compared to a previous measurement) could mean. As already indicated, the essence of this monitoring is that the measurements of the various indicators complement each other. Combining the results of monitoring these indicators provides valuable insight into the developments and trends in laboratory animal use and 3R developments.

#### **4.1.3. Data warehouse as a general source of information on laboratory animal use and 3R developments**

In addition to the aforementioned use of the data warehouse for monitoring indicators and making source data available as open data, the laboratory animal science field in the Netherlands would be

procedures. NCad is aware that the nature of this type of information differs from that needed for indicators, and that this information can be disclosed only if leaders in the research community are prepared to share it on a voluntary basis.

Links could also be made in this part of the data warehouse to other relevant databases that report on research or links to the relevant literature could be included. A precondition for this is that the data warehouse and the linked data would have to be adequately searchable.

#### 4.1.4. Evaluation of data

In principle, a rich data warehouse could be established in the above way, whose function is not limited to monitoring or knowledge-sharing. There would also be a plentiful source of data that could be used, in principle, for performing meta-analyses or evaluations of the effects of the policy or specific parts of it. In order to facilitate complex evaluations in the final data warehouse, attention must be paid to the standardisation of terminology such as '3R alternatives' in relation to 'development', 'use' and 'implementation'.

## 4.2. From content to implementation

The previous sections outline which data must become available from the data warehouse and how this could be used. The next sections describe how the data warehouse can be developed, and also cover feasibility, process management and supervision and a number of preconditions.

### 4.2.1. Feasibility

The proposed data warehouse does not have to be complicated from a technical ICT perspective, if it is built as a platform that links different data sources and has an adequate search function. The unique functionality for the manager consists of the software for calculating the indicators, insofar as these originate from different source files.

During the design of the data warehouse, it will have to be considered from an efficiency perspective whether the management organisation should be able to process the source data itself in order to make it suitable for inclusion in the data warehouse. This processing does not involve the data itself, but rather how it is stored. If it is decided to leave this up to the source data managers, strict arrangements regarding the delivery of data will be required. An investment on the side of the source data managers may also be necessary.

Based on the information that NCad has gleaned from consulting various parties, it estimates the initial investment for ICT and the other required organisational activities at several hundred thousand euros.

The management fee for the data warehouse and use of the indicators is estimated at two to three hundred thousand euros a year. This includes storing the data, delivering it twice a year, periodically entering data from source files, the management and continued development of the data warehouse, the necessary licences and reporting tools, and back-up options. Any new data sources can be connected relatively easily.

Compared to other employee and customer satisfaction surveys conducted by the government, it is realistically expected that a professional, systematically designed and periodically repeated 3R monitor will cost around 75 thousand euros every two years. The expansion of the data warehouse for the purpose of knowledge-sharing will require further investment, but this will be comparable to a data warehouse such as *Loket Gezond Leven* (Healthy Living Desk).<sup>3</sup> One condition, however, is that the research community expressly participates in this part, practically, substantively and financially.

In order to set the desired wheels in motion, NCad believes it would be advisable for the government to budget at least half a million euros a year over the coming years.

Although these are reasonable estimates, experience teaches us that the costs of such a comprehensive project with several data partners can easily increase. A definitively specified offer must therefore be drawn up after preliminary research is conducted in the first phase of the allocation of the project to the implementing organisation.

#### **4.2.2. Process management and supervision**

Although building a data warehouse is perhaps not difficult from a technical ICT perspective, it presents an organisational challenge

because of the different source data owners and the many people involved in the research community. Besides stocking the data warehouse and determining the quality of source data, substantive expertise in relation to the data is also required. A robust ICT

infrastructure is also a must. In order to build this in an efficient and effective manner, preference is given to the use of the DTAP model: Development, Testing, Acceptance and Production.

Based on exploratory talks with other organisations that have established similar data warehouses, NCad concludes that this requires a strict regime and proper process-based approach. Similar to the establishment of the *Informatiehuis Marien* (Marine Information Centre)<sup>4</sup>, this is to obtain a strong sense of involvement of all parties concerned and to lay a firm foundation for future development with leaders from the research community. For this reason, a party that can also be responsible later for drawing up trend reports, without holding any direct interest itself, and which enjoys the confidence of the research community, should be chosen to manage the data warehouse. Due to RIVM's role as the scientific adviser to the government, NCad believes it, or a suitable academic institution, would be an appropriate party for this purpose.

RIVM has experience in this area with data warehouses such as *Kosten van Ziekten* (Cost of Illness)<sup>5</sup>, *Voedselconsumptiepeiling* (Food Consumption Survey)<sup>6</sup> and *Loket Gezond Leven* (Healthy Living Desk) and has developed into the Data Authority within the government in the area of health, the environment and space. However, RIVM no longer has operational knowledge in relation to animal procedures such as that which is available in academic institutions.

In the process-based approach, it is important that adequate time is taken to develop the data warehouse and that this is done in two stages, as stated above, with the first stage being the collation of data

that is already available to the government, such as at the NVWA and CCD. From a process-based perspective, it is important to keep the two stages separate because they have different primary goals. Especially for this first part, it is important that source data suppliers are fully committed and help to direct the implementation. The basis of the data warehouse will be formed by data of the NVWA, CCD and, to a lesser extent, ZonMw. It is essential that the Minister requests these organisations to cooperate in building a data warehouse and to assign resources to it.

Because the data warehouse strives to achieve several goals, it is important that other parties are involved and participate from an early stage. It is crucial that the data warehouse is not just seen as a government instrument for and by the government. It must be a basis for everyone who is interested in animal procedures, so people feel supported by the available data.

The following steps must be followed in order to arrive at an effective data warehouse.

1. Stakeholder analysis: the expectations, wishes and requirements of all types of actual and potential interested parties need to be specified.
2. Assessment: the available sources, data and their quality are to be identified.
3. Design: in order to gain progressive insight and be able to incorporate interim changes in the development of the data warehouse, the interactive, functional and technical design is to

be worked out in steps (scrums). This will be followed by a visual design, in which user-friendliness is an important priority.

4. Development: the data warehouse is to be developed, connected to the external sources and, following optimisation, made available to the wider public.

#### **4.2.3. Preconditions for a properly functioning data warehouse**

The preconditions for working with data files in a data warehouse are that terminology must be standardised and the data warehouse must be structured such that it is searchable using logical search terms. Both elements still deserve a lot of attention.

Although terms are laid down in relation to formal laboratory animal registration, this does not mean they are always interpreted in the same way or also applied outside of registration in that way. There are moreover no unambiguous definitions or interpretations with regard to 3R developments, particularly for replacement alternatives.

NCad recommends taking the following principles as the starting point for monitoring 3R alternatives:

- **Alternatives for animal procedures** are methods or approaches that lead to a Replacement, Reduction and/or Refinement in the use of laboratory animals, also known as the 3Rs;
- A **Refinement alternative** means a method or approach that leads to a reduction in the distress of individual animals during the experiment, such as pain management, or to the enhanced welfare of individual animals, including through cage enrichment;

- **Reduction** means a reduction in the number of animals for answering a scientific question or, in the context of education, for achieving the learning objective. Reduction is linked to an animal procedure and can be implemented by using a new technology, such as telemetry, or through better design of the experiment;
  - **Replacement** means the method or approach that leads to the replacement of a laboratory animal by an alternative method to animal testing. Replacement by a ‘lower animal species’ is regarded as replacement only if it involves an animal species that is not defined as a laboratory animal by law;
  - An **alternative to animal testing** is always linked to a real change in the implementation of an existing animal model and results in one of the 3Rs. Methods or approaches that do not lead to one or more of the 3Rs therefore cannot be regarded as an alternative to animal testing.
  - Monitoring the effect of 3R alternatives is therefore linked to the measurable effect on laboratory animal use and thus to the licensed institution where this laboratory animal use occurs;
  - **3R effects can be direct** (such as replacing an animal procedure with a tissue culture method or reducing distress after applying pain management) **or indirect** (such as increasing the production volume of a vaccine batch so fewer animal tests are required for the control of that batch);
  - **Implementation of a 3R method** is a non-recurring event and implementation can therefore only be named as such on a one-off basis by a licensed institution in the 3R monitoring. In subsequent years, the 3R method applies as the standard model and is no longer referred to as an alternative method;
  - The **development and optimisation of a 3R alternative** can be a dynamic process, whose progress can be reported on in several subsequent years. In these cases, the penultimate 3R development is a reference point for identifying the 3R effect that has been achieved;
  - The **context must be taken into account when identifying the 3R effect**. For instance, a reduction in laboratory animal use can lead to an increase in the distress of individual animals (such as during the use of telemetry for which a surgical intervention is needed) and an in-vitro, pre-screening method for the selection of pharmaceuticals leads to an increase in the supply of potentially interesting pharmaceuticals for follow-up research on the basis of laboratory animal studies.
- A second important precondition, which is particularly important for the second goal of the data warehouse, is the existence of a proper search filter for literature reviews, by which all published 3R developments included in biomedical databases worldwide could be easily retrieved. Searching with an overly general filter introduces a lot of ‘noise’ into the search results (i.e. irrelevant studies), while an overly specific filter may not include all related articles. There is also an urgent need for 3R filters and search profiles with adequate distinguishing capacity.
- The development of an all-inclusive 3R or alternative filter for broad biomedical databases such as PubMed or Embase seems unattainable for the time being. However, there may be options for databases more specifically focused on the 3Rs. Both nationally and internationally,

various parties are working on the implementation or disclosure of 3R information, including Norecopa, Go3Rs, AWIC, CAMARADES, etc. Because these initiatives have not been introduced primarily for monitoring purposes, it is unclear which initiative (or combination of initiatives) would be best suited to join or expand on. To this end, an exploratory study into the feasibility of a general 3R filter on the basis of 3R databases, by joining other initiatives, is needed. This study would require an investment of around €25,000.00.

## 5. Appendices

### Appendix 1: Summary of recommendations from the advisory report ‘Indicators, management, and utilisation of data for monitoring laboratory animal use and 3R alternatives, Part 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<sup>4</sup>, 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<sup>5</sup>, 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”<sup>6</sup>;
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.

#### *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).

#### *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' 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 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.

## Appendix 2: Overview of indicators

*Reading guide: the table below indicates how a change in the indicators can be interpreted. The stated interpretations are not exhaustive. For each presentation of separate, monitored indicators, it is important to examine and explain their possible meaning, for example by combining them with evaluation or other indicators (triangulation).*

Monitoring indicator	An increase in the indicator compared to the last measurement may indicate	A decrease in the indicator compared to the last measurement may indicate	Parameters	Source	Missing link
Use of animals in animal procedures	Increase in laboratory animal use, change in the animal species used, increase in distress, incidental or structural change in research focus, broader definition of laboratory animal and animal procedure, increase in research questions	Absolute or relative replacement, refinement, incidental or structural change in research focus, narrower definition of laboratory animal and animal procedure, decrease in research questions	Year, number of animals, animal species, research objective, distress, etc.	NVWA	Make data more accessible as open data (transparency and reuse of data)
Animals killed in stock	Increase in the number of animals killed in stock, increase in laboratory animal use, increase in genetically modified laboratory animals (GM, mice and zebra fish), narrower margins (weight, age, sex) in requirements for the required laboratory animals, increase in genetic modification of animals species other than mice and zebra fish	Decrease in the number of animals killed in stock, decrease in laboratory animal use, decrease in genetically modified laboratory animals, better breeding policy, better matching of supply and demand in laboratory animals, wider margins (weight, age, sex) in requirements for the required laboratory animals	Year, number of animals killed in stock, GM share, animal species, etc.	NVWA	Make data available as open data (transparency and reuse of data)

Anticipated laboratory animal use	Increase in laboratory animal use, high estimate of required number of animals in project licence applications, increase in project licence applications (larger margins in number of required laboratory animals)	Decrease in laboratory animal use, low estimate of required number of animals in project licence applications, decrease in project licence applications (larger margins in number of required laboratory animals)	Year, planned number of animals, animal species, area of application, etc.	CCD	Transfer the data from the non-technical summaries (NTS), which is already open data, to a structured data storage facility
3R culture within licensed institutions	Improvement of 3R climate within the institution, improved insight into 3R developments within the institution, increase in 3R developments within the institution, increase in 3R knowledge among employees of the institution, altered research focus, decrease in obstacles (or more support in that regard) to 3R developments within the institution, subjective factors	Worsening of 3R climate within the institution, diminished insight into 3R developments within the institution, decrease in 3R developments within the institution, decrease in 3R knowledge among employees of the institution, altered research focus, increase in obstacles (or less support in that regard) to 3R developments within the institution, subjective factors	Vision/culture within the institution in relation to 3Rs, laboratory animal and 3R policy, impact, own efforts and possibilities, obstacles experienced, etc.	3R monitor	3R monitor to be developed
Evaluation indicator	An increase in the indicator compared to the last measurement may indicate	A decrease in the indicator compared to the last measurement may indicate	Parameters	Source	Missing link
'Anticipated laboratory animal use' – 'animals used in animal procedures' relationship (follows from a combination of monitoring indicators)	Larger margins in estimating the number of laboratory animals required in project license applications, application of Reduction during the course of the project	Smaller margins in estimating the number of laboratory animals required in project license applications, change in the procedure design during the course of the project	Year, number of animals, planned number of animals, animal species, research objective, distress, etc.	NVWA, CCD	

'Animals killed in stock' – 'animals used in animal procedures' relationship (follows from a combination of monitoring indicators)	Increase in animals killed in stock, decrease in total laboratory animal use, increase in share of genetically modified animals within the total number of laboratory animals used	Decrease in animals killed in stock, increase in total laboratory animal use, decrease in share of number of genetically modified animals within the total number of laboratory animals used	Year, number of animals, animal species, research objective, distress, number of animals killed in stock, share of genetically modified animals, animal species, etc.	NVWA	Make data available as open data (transparency and reuse of data)
'Anticipated degree of distress' – 'actual degree of distress among animals used in animal procedures' relationship	Increase in research with greater distress, change in distress classification, increased insight into pain management, specific animal species (such as fish)	Decrease in research with greater distress, increased use of pain management and anaesthesia, change in distress classification, application of Refinement in animal procedures (during the course of the project), increase in application of humane endpoints	Year, number of animals, planned number of animals, planned distress classification, distress classification, application of anaesthetics and analgesics, animal species, research objective	NVWA, CCD	Make data available as open data (transparency and reuse of data)
Performance indicator for promising developments in 3R alternatives	Improvement in climate for 3R development, increased interest in and visibility of 3R developments, validation/acceptance of new 3R alternatives, better acknowledgement and recognition of 3R alternatives	Worsening of climate for 3R development, less interest in or visibility of 3R developments	Breakthrough technologies	Publications, expert consultation, opinions (trade associations), targeted studies	Clear definition of key concepts (3R alternatives)

Performance indicator for financing 3R alternatives	Increase in research budget for 3R development, improved insight into the impact of 3R developments, more efficient 3R research.	Decrease in research budget for 3R development, decreased insight into the impact of 3R development	Budget and impact	Grant institutions, RIVM, institutions (earmarked 3R budgets)	Make data available as open data (transparency and reuse of data) Develop a method with financers for generating performance indicator (ZonMw, etc.)
Performance indicator implementation 3R alternatives	Improvement in climate for 3R developments, increased interest in and visibility of 3R developments, validation/acceptance of new 3R alternatives, better acknowledgement and recognition of 3R alternatives, subjective factors, increased accessibility to 3R alternatives, broadening of the definition of 3R alternatives	Worsening of climate for 3R development, less interest in or visibility of 3R developments, reduced acknowledgement or recognition of 3R alternatives, subjective factors, narrowing of the definition of 3R alternatives, greater return to traditional research methods	What is available and what is applied?	Expert panels for each domain (annually), IvDs, ZonMw, ECVAM, RIVM	Clear definition of key concepts (3R alternatives) Prepare search functions and search questions
Perspective index for each animal species and area of application	More or more influential newly validated/accepted 3R methods (anticipated), quicker route to the application of 3R alternatives	Less or less influential newly validated/accepted 3R methods (anticipated), longer route to the application of 3R alternatives	Where is this leading to, and at what expected rate?	Expert panels for each domain (every two years)	To be set up
Performance index for effect of policy and investment	More effective 3R policy than other comparable licensed institutions	Less effective 3R policy than other comparable licensed institutions	Resources (FTEs and financial) used by licensed institutions for animal procedures, resources (FTEs and financial) used by licensed institutions for 3R research, output, impact	Expanded 3R monitor, scientific publications, reports, annual reports and progress briefings on animal laboratory science standardised by means of the <i>Code Openheid</i> (Transparency Code)	To be set up in two stages in consultation with the research community

## Appendix 3: Recommendations arising from the consultation of community groups

During a meeting held on 14 January 2016 in The Hague, the Biomedical Primate Research Centre, Hartstichting, Proefdiervrij, ZonMw, NVDEC, NVP, NFU, WIL Research, Beroepsgrond Proefdierdeskundigen, HollandBio, Stichting Stimuleringsfonds Alternatieven voor Dierproeven, Denktank IvDs, SYRCLE, and 3Rs Centre ULS provided input for this advisory report as part of the societal expert group on animal procedures and alternatives (MEDA). PETA provided its written input prior to this meeting.

NCad extracted recommendations from the audio recordings of the meeting, which were then submitted for approval and any clarification to the relevant groups. Their agreed recommendations are set out for each topic below, with an indication in each case of whether a particular recommendation has been included in NCad's advisory report. Where this is not the case, a short reason is provided.

The recommendations that groups made during the social consultation on Part 1 of the advisory report, but which related to topics covered in this Part 2, are presented separately.

### Indicators

*Nederlandse Federatie van Universitair Medische Centra (NFU)*

- also pay the necessary attention in the monitoring to Refinement within the principle of Culture of Care. Much is being achieved in that area and it also implies that most laboratory animals have a good quality of life (also because of the high requirements that are set for their accommodation and care) (included in the advisory report)
- devise a way to obtain a clearer picture of the impact of replacement alternatives (the development and implementation of methods); these are events that happen quickly but their impact on animal procedures is then unclear; moreover, the majority of these types of developments are not labelled as an 'alternative to animal use' (included in the advisory report)

*Denktank IvD's*

- try to provide insight into the value of animal procedures by monitoring the number of cases in which the research objective is achieved with animal procedures (included in the advisory report)

*Nederlandse Vereniging voor Proefdierkunde (NVP)*

- see the licensed institutions, DECs and IvDs as the main sources of information for data on Refinement (included in the advisory report)
- monitor the number of articles published for each research objective, including the number of laboratory animals used, every five years. This can be an indicator that invisible alternatives are or are not being implemented in that research objective area. This can then be specifically investigated. This is a rough, but useful indicator. By comparing research objective areas with each other,

- policy could be focused on those areas in which little development is evident (included in the advisory report)
- investigate the possibility of using resources (budget, FTEs, etc.) in relation to monitoring animal procedures (at macro level). If this relationship was ‘more favourable’, one could assume that invisible alternatives are one of the drivers behind that development. After all, the research questions in biomedical science have not essentially changed (included in the advisory report)

#### *Biomedical Primate Research Centre (BPRC)*

- be very cautious in the use of the 3R budget as an indicator. This can very quickly lead to disputes, despite the standardisation of definitions. Moreover, 3R budgets that are needed to implement the 3Rs can differ very widely for each field of study or even for each animal species (particularly in relation to refinement) (included in the advisory report)
- identify indicators for the expectations relating to the 3Rs ‘where are we going?’ (included in the advisory report)
- keep things simple when starting to make a dashboard with indicators (included in the advisory report)

## **Data warehouse**

#### *Nederlandse Federatie van Universitair Medische Centra (NFU)*

- realise that the Netherlands is a small country and that most developments, including in the area of the 3Rs, occur outside the Netherlands; without an international dimension, ambition is, by definition, also limited (included in the advisory report)

#### *Denktank IvD’s*

- report cases, so people can learn from each other (included in the advisory report)
- explain which registered data is not published in *Zo doende* (not included in the advisory report, forms part of the assessment phase during the development of the data warehouse)
- bring groups of similar licensed institutions together to help obtain data sets (not included in the advisory report, but will be taken into account as a practical recommendation in case of implementation in the second stage)
- bear in mind that some institutions work outside the sight of the IvD on 3R alternatives (Replacement) (included in the advisory report)
- a data warehouse is valuable for monitoring and for intelligent evaluation and trend analyses. It is also advisable to set up a different system at IvD level, in which findings, knowledge and CoPs can be exchanged in an easily accessible manner (not included in the advisory report, as it falls outside the scope of the request for it)

#### *Beroepsgroep Proefdierdeskundigen*

- link the various accounts that are kept in the public domain with each other (included in the advisory report)
- explain where and how institutions currently make their data available (included in the advisory report)
- keep the goal in mind when dealing with questions on input and communicate this clearly. Do not gather data haphazardly, ask yourself first what information you want and for what purpose. Then search for the correct indicators that could shed light on this (included in the advisory report)

## NVDEC

- does the data warehouse give the DECs a function in their statutory duty to verify the availability (or absence) of 3R alternatives to animal procedures? (included in the advisory report)
- when designing the data warehouse, focus on the demand for information; what does society wish to know about laboratory animal use and the 3Rs?(included in the advisory report)
- do not prioritise one of the 3Rs, but rather prioritise by research objective area and try to disclose data within that area (included in the advisory report)
- use the annual report that some DECs publish as a source of information (included in the advisory report)

## Evaluation

### *Nederlandse Federatie van Universitair Medische Centra (NFU)*

- changes become clear from the statistical data on laboratory animal use. The new system is also far more detailed than the previous one. By questioning experts about these changes, insight can be increased (including through the identification of drivers, which are often technological developments (included in the advisory report)
- trade associations can assist in gaining some insight into 'hidden 3R developments', particularly reduction and refinement (included in the advisory report)
- try and gain insight into the life cycle of 3R alternatives. Some | 3R alternatives seem promising and are tested in several locations, but quickly fall into disuse. This must also have an impact on the content of the available databases, etc. (included in the advisory report)

## *Beroepsgroep Proefdierdeskundigen*

- by monitoring fields of study (research objective areas) that are determined each year, try to gain insight into 'hidden 3R developments'. This produces a broader picture than focusing on the areas in which animal procedures take place (included in the advisory report)
- make use of welfare evaluations and the laboratory animal policy of different licensed institutions and their output/impact (cf. Access to Medicine Index) for increasing insight (included in the advisory report)

## *SYRCLE*

- make use of the annual reports on laboratory animal science by licensed institutions for analysing Refinement (included in the advisory report)
- request the licensed institution to give insight into the budget that is spent on 3R. Merely asking the question already creates awareness (included in the advisory report)
- see the statistician within the IVD as an important person for obtaining insight into developments within the institution (not included in the advisory report, relates to authorisation by the licensed institution. Will be included as a recommendation in any creation and specification of target groups of the 3R monitor)

## *HollandBio*

- before the data warehouse is designed, pay attention to the question of who is going to analyse the data in the data warehouse and for what purpose (included in the advisory report)

### *WIL Research*

- make use of experts to put trends that are identified in quantitative data into the correct perspective (included in the advisory report)
- take international developments into consideration (which alternative tests are recommended or prescribed by regulation) (included in the advisory report)

### *Stichting Stimuleringsfonds Alternatieven voor Dierproeven*

- consider including in the data warehouse which initiatives (budgets) exist in the 3R area in the Netherlands (included in the advisory report)

### *Biomedical Primate Research Centre (BPRC)*

- make use of trade associations to increase insight into each research objective area (included in the advisory report)

### *PETA*

- perform regular evaluations of developments in alternatives to animal testing (through continuous professional development within the CCD and by monitoring updates of testing directives and recommendations of EURL ECVAM (included in the advisory report)
- pursuant to Article 58 of Directive 2010/63/EU, conduct regular thematic reviews of data originating from animal procedures. To this end, establish a framework to review the use of specific animal species in specified areas of research and procedures in each case. Also use separate frameworks for statutorily prescribed procedures and scientific research (included in the advisory report)

## **From content to implementation**

### *Nederlandse Federatie van Universitair Medische Centra (NFU)*

- weigh up the ambition against the costs and required efforts of the data warehouse manager and suppliers and also consider the risks (being bogged down by ambition, lack of opportunities to do this for a longer period) (included in the advisory report)
- take the aim of creating a level playing field for scientific research in Europe into consideration in the recommendations (included in the advisory report)
- pay attention to the standardisation of definitions; if a researcher switches to an alternative to animal testing, the institution may register this method as a replacement alternative. This method subsequently becomes best practice in most cases and invisible in the statistical reporting (included in the advisory report)
- licensed institutions are aware of the need for social accountability and implement this themselves. Do not take this away from them through government centralisation (included in the advisory report)

### *Denktank IvD's*

- incorporate new 3R alternatives in Codes of Practice (not included in the advisory report, beyond its scope)

### *3R Centre ULS*

- pay attention to the standardisation of defined terms, particularly as regards 3R alternatives (included in the advisory report)
- weigh up whether the time and energy needed for the monitors are compensated for by the use of the collated data (included in the advisory report)

- refine the purpose for which data on animal procedures and 3R methods must be collated (and made available) (included in the advisory report)
- ensure that licensed institutions can enter their data directly into the data warehouse, via a standardised system (not included in the advisory report, forms part of the design phase of the data warehouse's development)

#### *SYRCLE*

- make use of the Transparency Code, which has been signed by a large number of licensed institutions, for standardising data in the annual report on laboratory animal science by institutions. This includes elements that a licensed institution would have to include in the annual report on laboratory animal science. However, the specific content of the Transparency Code is for each party to establish itself, as a result of which every annual report is different and includes different elements. Standardisation is important. This code can easily be extended to all licensed institutions and, through standardisation, would facilitate comparison among them (included in the advisory report)
- start with analysing the Replacement and Reduction of animal procedures because these developments are very difficult to analyse, but easier to get a grip on than Refinement (included in the advisory report)
- avoid reinventing the wheel in relation to data on 3R alternatives in the data warehouse. Coordinate with European forums in this area, such as the various umbrella 3R databases that are available (included in the advisory report)

#### *HollandBIO*

- provide clarity on the purpose(s) of monitoring and of the data warehouse. Determine beforehand which data you actually need for analysis and collate only that data. In this way, registration is on a need-to-know basis and you avoid ultimately getting bogged down in excessively collated nice-to-know data. It is also then clear to the suppliers of the data that something will be done with it and why they must deliver the data (included in the advisory report)

#### *Nederlandse Vereniging voor Proefdierkunde (NVP)*

- bear in mind when designing both monitoring (and accompanying) indicators and the data warehouse that society is mostly interested in Replacement (included in the advisory report)
- be clear about the purpose and expectations of monitoring and the data warehouse. Scientists will continue to focus on scientific publications for gathering knowledge, not on this data warehouse (included in the advisory report)

#### *WIL Research*

- pay attention to making data available on a standardised basis to avoid double/extraneous work. Only collate data to answer the question (e.g. what alternative [in vitro] tests have been worked on in the reporting period? and provide laboratory animal numbers for period y [as for Zo doende]) (included in the advisory report)

#### *Stichting Stimuleringsfonds Alternatieven voor Dierproeven*

- identify and develop specific (or more specific) initiatives in the area of Replacement (identifying initiatives is included in the advisory report, but developing initiatives falls outside its scope)

## PETA

- make project licence applications publicly available before they are granted, to take account of a wider ethical and scientific review by independent, external experts (not included in the advisory report). The Experiments on Animals Act provides a strict template for dealing with individual project licence applications, including the ethical review and the applicable statutory periods. A broad, third and public evaluation of project applications does not fit within those time frames)
- enforce the statutory obligation to avoid animal procedures as far as possible (not specifically included in the advisory report, enforcing compliance with the law falls outside its scope)

## **Visions already stated during the consultation of community groups on Part 1 that related to Part 2**

### *The structured collection and provision of data*

#### *Nederlandse Vereniging voor Proefdierkunde (NVP)*

- weigh up whether the required significant efforts produce the intended result (included in the advisory report)

### *Better utilisation of available data*

#### *Koninklijke Nederlandse Akademie van Wetenschappen (KNAW)*

- a clear definition of 3R alternatives, in order to avoid differences in interpretation, is essential for data storage and monitoring (included in the advisory report)

#### *Three Rs Alternatives Initiating Network (TRAIN)*

- ensure that there are enough positive stimuli and opportunities for industry (often very large international companies) to disclose information on 3R alternatives (included in the advisory report)

#### *WIL Research, on behalf of the industry*

- opt for an approach based on the question whether 3R alternatives are used ('we use test x') or derived from the savings that are achieved ('We previously carried out 100 tests a year on three rabbits each time. Now we make use of in-vitro tests and save 300 rabbits a year as a result') or a combination of both (included in the advisory report)

### *Improving the accessibility of data*

#### *Biomedical Primate Research Centre (BPRC)*

- do not try to impose additional obligations on the grant institutions (usually European or international), such as the researcher having to make all raw data from animal procedures available (included in the advisory report)

*Nederlandse Vereniging voor Proefdierkunde (NVP)*

- take mainly the numbers that are already registered as the starting point for data storage and monitoring, extract trends from these and perform any meta-analyses on them. Do not impose any additional obligations on the research community (included in the advisory report)

*Nederlandse Federatie van Universitair Medische Centra (NFU)*

- be aware of the different evaluation methods that are going to be used when trends in changes are examined (included in the advisory report)

*WIL Research, on behalf of the industry*

- ensure that licence holders, if asked to report on savings made through replacement and reduction alternatives in regulatory research, only mention the savings in relation to the directives in force at that time (included in the advisory report)

*Other comments*

*Nederlandse Federatie van Universitair Medische Centra (NFU)*

- bear in mind that this ambition cannot lead to an increase in the statutory requirements for data provision or other activities. The European Directive prohibits further requirements being set in relation to the regulations that applied before 10 November 2010 and Directive 2010/63/EU (included in the advisory report)

## Footnotes

- 1 <http://www.ncadierproevenbeleid.nl/adviezen-ncad/documenten/rapport/2015/11/1/ncad-advies-dataopslag>
- 2 Classification of research domains, as included in the implementing decision of the European Commission of 14 November 2012, [notified under document C(2012) 8064], Annex 2 under purposes of research.
- 3 Loket Gezond Leven (Healthy Living Desk) and Gezonde School (Healthy School) provide guides for health promotion in the municipality and community, at school or work. The *Interventiendatabase Gezond en Actief Leven* (Intervention Database for Healthy and Active Lives) provides insight into the range and quality of lifestyle interventions. <https://www.loketgezondleven.nl/>
- 4 The purpose of *Informatiehuis Marien* (Marine Information Centre) is to make all data, information and research data on the North Sea accessible to interested parties, authorities and professionals in one place. <http://www.informatiehuismarien.nl/>
- 5 *Kosten van Ziekten* (Cost of Illness) is a numerical tool with figures on the cost of healthcare in the Netherlands, based on the RIVM's 'Cost of Illness in the Netherlands' study. <https://www.volksgezondheidenzorg.info/kosten-van-ziekten>
- 6 The *Voedselconsumptiepeiling* (Food Consumption Survey) contains data on food consumption and the nutritional status of the Dutch population in general and separate population groups in particular. <http://www.rivm.nl/Onderwerpen/V/Voedselconsumptiepeiling>

## We would like to thank the following experts

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Stakeholders and chain partners are also consulted.

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