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

Transition to non-animal research

on opportunities for the phasing out of animal procedures and the stimulation of innovation without laboratory animals

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

The NCad and its methods

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

Members of the NCad

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Summary

World leader in innovations without laboratory animals by 2025. That is the aim of the Dutch Minister for Agriculture, Martijn van Dam. In March 2016, the Minister asked the Netherlands National Committee for the protection of animals used for scientific purposes (NCad) to draw up a schedule for the phasing out of animal procedures.

Initially, this request caused consternation among those involved with animal procedures. This was evident from the two workshops run by NCad in June and July and from the public consultation that took place in September. The use of animals for research and education is a highly complex issue, particularly given the diverse and at times conflicting interests involved. Much of our current understanding of the way the body works and the causes of and treatments for illnesses derives from research that involved experiments on animals. But these animal procedures have gone hand in hand with animal suffering that ranged from mild to substantial. Based on the input of the many experts consulted and its own expertise, the NCad has produced the following opinion: 'Transition to non-animal research methods – *On opportunities for the phasing out of animal procedures and the promotion of innovation without laboratory animals*'. This opinion contains specific recommendations for accelerating the transition from animal procedures to innovative non-animal research methods.

Although there is scientific, economic and social potential for innovations without laboratory animals, according to the NCad, these are currently not being sufficiently exploited to promote and accelerate the transition process. Only with a broad-ranging and coordinated effort by the ministries involved and other stakeholders can significant progress be made in reducing the use of laboratory animals in research.

The NCad makes recommendations under three different themes: Clear transition objectives, Transition strategy and Management of the transition.

Clear transition objectives

If we are to make the transition to non-animal research methods, we must make a paradigm shift away from existing mindsets and practices. That way, says the NCad, we can focus heavily on innovations without laboratory animals in a number of fields in the period up to 2025. In the case of *regulatory research*, the NCad sees potential for a significant reduction in the use of laboratory animals. The use of laboratory animals in regulatory safety testing of chemicals, food ingredients, pesticides and (veterinary) medicines can be phased out by 2025, whilst maintaining the existing safety level. The same applies to the use of laboratory animals for the release of biological products, such as vaccines. At this stage, regulatory pre-clinical research cannot be phased out at the same pace.

In the field of *fundamental scientific* research, the opportunities for a substantial reduction in the use of laboratory animals vary from one field to another. The NCad recommendation to the Minister for Agriculture concerns the development of a ten-year vision for each area of fundamental scientific research (or for each cluster of disciplines) in consultation with the public and the scientific

community. These visions must include clear transition objectives that are linked to the core focus of the area of research concerned. They must also give an insight into the potential of innovations without laboratory animals in these areas.

The NCad believes that, in the field of *applied and translational research*, more rapid progress can be made than is being made at the present time. There is a great deal of innovative potential that could be better exploited. In this context, the NCad advises the Minister for Agriculture to focus more heavily on innovations without laboratory animals, amongst others in the field of the development of human models for human diseases and by promoting cross-sectoral and multidisciplinary collaboration on innovation policy. That way, the Netherlands can be an international leader in the field of innovations without laboratory animals in this area of research by 2025.

The use of laboratory animals in *education and training* can be significantly reduced. The NCad points in this context to alternative teaching models and ethical reflection, i.e. changing the mindset of young professionals with regard to the use of animals. The NCad recognises that the use of laboratory animals in training professionals involved in the field will continue to be necessary to a certain extent, but believes that, here too, cultivating a mindset that does not rely on laboratory animals will help keep the number of animal procedures to a minimum.

Transition strategy

- By promoting innovations without laboratory animals and exploiting them to the full, the use of laboratory animals can be reduced. The NCad has formulated a number of strategic recommendations that may help to speed up the transition process. The NCad offers the Minister for Agriculture the following recommendations:
- Work at the international level to obtain a review of the regulatory risk assessment process. Given the international nature of this area of research and the regulations involved, a new approach to risk will only succeed in the context of major international collaboration;
- Make the Ministry of Economic Affair's innovation policy more chain oriented, in order to encourage multidisciplinary collaboration and to allow promising innovations without laboratory animals to progress more easily from development to actual application;
- Invest in the valorisation and acceptance of non-animal testing methods, e.g. through backward validation studies.;
- Ensure that better use can be made of data from human subject research. The options in this context should should be investigated further by a designated party;
- Invest in risk communication and the investigation of risk acceptance. The effective protection of people and animals will benefit from a modern approach to risk management. The NCad's recommends the adoption of a radically different approach to risk. In this context, it is important that the extent to which health risks are safeguarded by the chosen research methods is made more transparent;

- The Minister for Agriculture should, in the context of the transition strategy, monitor, evaluate and disseminate knowledge around innovation without laboratory animals and 3R alternatives. The NCad advises the Minister to make monitoring and evaluation of the phasing out of animal procedures a priority, and refers in this context to its earlier recommendation on the development of a data warehouse. The NCad also believes that it would be a good idea to create an Innovations Without Laboratory Animals Index in collaboration with other countries, along the lines of the Access to Medicine Index.

Management of the transition

The transition to non-animal research methods will not happen on its own; it will require management and focus. International collaboration involving all stakeholders is the key to success. The NCad advises the Minister for Agriculture to play a guiding role in the process, and to also involve other ministries in order to ensure that a consistent and coherent policy is developed at national level. Transforming the Interdepartmental Working Group on Alternatives to Animal Procedures (*Interdepartementale Werkgroep Alternatieven voor Dierproeven*) into an Interdepartmental Management Group will ensure that work is consistent and collaborative and that the policy on the use of animals in research is linked to other policy issues. In addition, the NCad recommends establishing an Agenda for Innovation Without Laboratory Animals as a new route within the National Science Agenda, based on a joint approach by all national stakeholders. This Agenda for Innovation Without Laboratory Animals must focus on specific objectives that are both ambitious and achievable.

The NCad believes that the Netherlands is in a unique position to promote itself at international level as a leader in the field of innovations without laboratory animals. This position can be used to speed up the transition to non-animal research methods at international level also.

Keywords

Transition, animal procedures, reduction, phasing out, phase out, 3R alternatives, innovation without laboratory animals, regulations.

"The world as we have created it is a process of our thinking. It cannot be changed without changing our thinking."
Albert Einstein

Contents

1. Introduction

The use of animals for scientific purposes and education and for testing the safety, quality and efficacy of substances has a long history. Experiments involving animals were carried out as far back as the fifth century BC, primarily in order to describe biological systems that at that time were still unknown. Much of our current understanding of the way the body works and the causes of and treatments for illnesses derives from research that involved experiments on animals. In the 21st century, animals are used as a research model for humans and, if veterinary research is involved, for example, also as a model for animals. At the same time, we are witnessing rapid developments in technology. Animals are also used in the context of biological field research, for the production and release of biological products (such as serums and vaccines), for skills training and for educating doctors, vets and other professionals. Every year, some 11.5 million laboratory animals[1] are used in Europe, about 563,769 of which are used in the Netherlands (2014). In the Netherlands, animal procedures are carried out for regulatory purposes (25.8% in 2014, of which: 9.5% toxicity tests for veterinary medicines, 8.6% for human medicines and 5.4% for industrial chemicals), in the context of applied and translational research (32.1%), in the context of fundamental scientific research (27.6%) and in education (3.2%) and breeding of animals with discomfort (10.5%) [2].

The principles of the 3Rs[3] (Replacement, Reduction and Refinement) were developed some sixty years ago as a framework for the use of animals in research. In recent decades, they have become an integral part of legislation and regulations[4] and scientific experiments involving animals in the Netherlands and the EU. They aim to prevent the use of animal procedures[5] where an alternative that does not involve animals is available. They also aim to ensure that research is conducted in such a way as to minimise the use of animals and to cause as little discomfort, pain and stress to animals as possible, whilst retaining the scientific quality of the research. The research community is working hard on the further development and implementation of 3R methods. Since the current laboratory animal registration system was introduced in the Netherlands in 1978, the use of laboratory animals in the Netherlands has decreased by approximately two thirds [6].

After a sustained downward trend over many years, the number of animals used annually in animal procedures in the Netherlands has remained stable in recent years at around 550,000. Over that period, the volume of scientific research has increased. In other words, it appears that relatively fewer animals are used for a larger research output. The impact of 3R approaches on this relative decrease cannot be identified clearly at this stage. In its opinion “Indicators, management and utilisation of data for monitoring laboratory animal use and 3R alternatives”, the NCad recommends increasing insights in this field, amongst others by establishing a data warehouse around the use of animals in scientific procedures.
The question frequently arises in both public and political spheres as to whether it is possible to carry out research without the use of animals or with the use of far fewer animals. Moreover, in recent years, an increasing number of academic publications have suggested that the predictive value of animal models for certain disease

processes in humans is variable. Animal models are better for some disease processes than they are for others. This underlines the importance for the value of animal models and other research models to be periodically reviewed by the scientific community.

The government has been pursuing a policy that aims to reduce the number of animal procedures for some time now, albeit with a limited budget. This includes making access to knowledge more efficient and promoting innovations that do not involve animal procedures through national and European grant programmes. In addition, since the end of 2014, the Dutch legislation in this field, which previously involved animal procedures being ethically assessed by Animal Ethics Committees (DECs), has been converted into a regulatory system that involves the awarding of licences for projects involving animal procedures. Here, an ethical assessment is made of the social and scientific benefits as compared with the use of animals and the associated suffering. When making this assessment, the Central Authority for Scientific Procedures on Animals (CCD) takes advice from the DECs.

In the case of many animal models, there are as yet no replacement methods. Moreover, it should be noted that, for practical and legal reasons in particular, many innovations without laboratory animals still struggle to progress from development to application. As a result, many opportunities for reducing the use of laboratory animals are insufficiently recognised[7] and are not exploited. And accepted alternative methods are often not applied consistently.

The debate between the various stakeholders around the use of animals in animal procedures is a heated one. This is an extremely complex issue (a wicked problem)[8] that can be compared, for example, with the debate and issues around climate change and the energy transition that is required as a result. There is little common ground between the many stakeholders involved and the debate is generally conducted in an atmosphere of mistrust.

The issue is also complex on account of the diverse and at times conflicting interests involved. Society needs safe products for consumers and the environment and new methods of treatment for patients. At the same time, it is important to keep the use of animals in research to a minimum. A key question in this debate is how the government intends to safeguard the risks to patients and citizens when commissioning new and existing products and when testing new methods of treatment. In the past, this question may not have been asked in a clear enough way. A second key question concerns the proportion of animal procedures that can be replaced by accepted alternatives or alternative research strategies whilst maintaining the current level of protection (in the case of regulatory testing) and scientific quality.

The multitude of factors and causes means that there is not a single party that can be designated as having sole responsibility for the use of laboratory animals. Moreover, the issue of animal procedures is closely linked with other issues and has an international context, which means that (rapid) change is often not forthcoming. And a sense of urgency with regard to the implementation of changes in the field of animal procedures often appears to be lacking among researchers and the government too.

And, whilst defining the highly complex issue of animal procedures is hard, defining the potential for reducing or phasing out animal procedures is even harder, because:

- the interests of animal welfare are often at odds with the interests of public health, and both are increasing in importance within society;
- a wide variety of different interests are at play in the implementation of animal procedures and, as a result, there are many players with a specific sub-interest: from patients, consumers, industry and knowledge institutions to animal welfare organisations;
- the actual fundamental scientific research is difficult to define;
- the debate is socially charged and gives rise to strong emotional responses;
- during the development phase, the promotion of new methods that could potentially reduce the number of animal procedures may lead to additional animal procedures and, as a result, public resistance will continue unabated during the development and validation phase;
- the use of laboratory animals cannot be reduced or phased out in isolation because the regulations around animal procedures are defined at European and, sometimes, international level. Moreover, both knowledge institutions and business and industry operate in international consortia and markets. The influence of the Dutch government is related to this European and international arena. This requires a strong lobby and the formation of a coalition;
- any mandatory policy that aims solely to reduce the use of laboratory animals in the Netherlands, where the 3Rs are firmly embedded in legislation and regulations and applied in all research involving animals entails the risk of high-quality research moving abroad, where animal welfare may well be considered less important;
- In the existing system the availability of funding for innovation without laboratory animals is relatively limited and fragmented.

Transition thinking and the multi-level perspective (MLP)

Given the nature of a wicked problem, taking an approach that is based on existing patterns will not lead to sustainable solutions in the foreseeable future. A more radical change in the way we think, act and organise is required: this is the core of a transition. This was also made clear in the report "In transition" that was published by the Think Tank on Supplementary Financing for Alternatives to Animal Procedures (Think Tank) in 2015. One of the analytical base models from transition research is a multi-layer model known as the Multi-Level Perspective (MLP). This model, which was developed by Frank Geels, makes a distinction between the following three levels to describe a system in which a complex issue requires solutions:

- ***the landscape:*** in which can be found major social changes in the field of politics, culture and world views (e.g. globalisation and individualisation) or natural characteristics over which little influence can be had and that are generally slow to change. Landscape developments are the result of ideas and action by large numbers of players;
- ***the regime:*** the structural level that forms the context of prevailing practice. This relates to the dominant culture, formal and informal rules, routines, knowledge and infrastructure that perpetuate a particular practice;
- ***niches:*** innovative social, economic, technological or policy practices that depart from and are protected from the dominant regime.

Within each of these layers, movements that affect thinking concerning the use of animals for scientific research and the use of laboratory animals can be identified. Transitions can be initiated and implemented through activities (interventions) and developments on the various levels, which then impact on each other. So, in the case of a transition, you have to learn the art of constantly "doing three things at once". Appendix 1 looks at the MLP in more detail, and Appendix 2 specifies factors and movements that influence the use of laboratory animals on the basis of the MLP.

In this report, the MLP is used to formulate an opinion on the measures to be taken in order to achieve a substantial reduction in the use of laboratory animals. All stakeholders have a responsibility here, and certain efforts are required from each of them. But the government is the only party that can manage the process, by bringing the parties together and uniting them under a common objective. Section 2 contains the request for an opinion and the associated response from the NCad. Section 3 contains the recommendations, grouped within three themes: "Clear transition objectives", "Transition strategy" and "Management of the transition". The recommendations are further underpinned in Section 4.

In addition to the above-mentioned information based on MLP thinking, the appendices also include a description of the knowledge in this field contained in existing documents, the consultations that took place prior to issuing of the opinion and the input that was provided.

2. Request for Opinion

On 8 April 2016, on the basis of an opinion issued by the Think Tank, the Minister for Agriculture, Martijn Van Dam, expressed in a letter to the NCad the aim that the Netherlands should be world leader in innovation without laboratory animals by 2025. In this letter, he asked the NCad for an opinion on how this could be achieved.

On 12 October 2015, I received an opinion from the think tank on Supplementary Financing for Alternatives to Animal Procedures entitled "In Transition! The Netherlands leads the way in innovations without laboratory animals" ("In Transitie! Nederland internationaal toonaangevend in proefdiervrije innovaties"). I support the ambition formulated in the think-tank's recommendation that the Netherlands should be the world leader in innovations without laboratory animals by 2025.

I have approached the NCad regarding the implementation of a section of this opinion. I request that you draw up a phase-out timetable for animal procedures. For brevity's sake, I refer you to the think-tank's opinion on which my request to you is based. Sections of the opinion that are also being implemented concern the creation of a fund for innovations without laboratory animals and the establishment of a support project office.

I wish to ask you to consider the following when drawing up the phase-out timetable:

- *that the transition perspective (see think-tank's opinion) and the international perspective is maintained;*
- *that the timetable is drawn up in full-fledged cooperation with the National Institute of Public Health and Environmental Protection (RIVM) and the Dutch Society for the Replacement of Animal Testing (Proefdiervrij). The involvement of the Dutch Society for the Replacement of Animal Testing will guarantee close alignment with the think-tank's opinion. I consider the direct involvement of the RIVM to be very important, given this organisation's expertise in the area of toxicity tests and its role as a national and international coordinator of the promotion and acceleration of validation, regulatory acceptance and implementation of 3R methods that can be used to determine the safety and/or effectiveness of chemical substances, medicines and vaccines;*
- *that those working in the field of animal procedures and alternatives to animal procedures be taken into consideration;*
- *that attention be given to the feasibility of the alternatives as well as priority sectors (very important for taking effective action in the international arena). With respect to the prioritised tests that are already included in the validation phase or will be added to it in the near future, I request that you draw up an action plan with the aim of accelerating validation, acceptance and implementation. Such a plan should be a permanent part of all alternatives considered within the context of the phase-out timetable;*
- *that concrete objectives are specified in the context of the phase-out. For example, over the next ten years, I would like to phase out the legally required toxicity tests, which account for approximately 10% of animal procedures.*

Questions raised in this regard are how the intended phase-out can be accomplished and what international efforts will be required in this regard? In summary, I request that you draw up a comprehensive plan that includes all relevant facets needed to achieve the phase-out.

I also request that, in drawing up the plan, you refer to the previously published reports and documents, such as the RIVM report Problems in developing, validating and implementing Alternatives to Animal Procedures (Knelpunten bij de ontwikkeling, validatie en implementatie van Alternatieven voor Dierproeven), the Business Case for Alternatives to Animal Procedures and

the Analysis of the Business Case for Alternatives to Animal Procedures (de Businesscase Alternatieven voor Dierproeven en de Analyse Businesscase Alternatieven voor Dierproeven), the response of the Regular Consultation Platform on Animal Procedures and Alternatives (RODA) dated 30 October 2014 to the Analysis of the Business Case for Alternatives to Animal Procedures and the recent assessments by the RIVM regarding possible legal impediments to the use of alternatives to animal procedures in the area of chemical medicines, biologicals and vaccines as well as in the area of chemical substances.

I ask that you prioritise the preparation of the phase-out timetable over other current requests for opinions and send me your detailed plan no later than October 2016."

On 2 May 2016, the NCad forwarded the following response to the Minister for Agriculture:

The Netherlands National Committee for the Protection of Animals Used for Scientific Purposes (NCad) has noted with interest the Minister for Agriculture's request for opinion regarding a phase-out timetable for animal procedures.

The NCad considers this a bold and ambitious request that it certainly wishes to pursue. However, the NCad believes that the time frame indicated is extremely tight for developing a detailed phase-out timetable that can count on broad support in the field through input from relevant experts and stakeholders.
In view of this short period, the NCad sees no possibility of internationally assessing and garnering support for its ideas regarding a phase-out, other than in a very limited context. Such an assessment will be necessary in a later stage, given the intensive international collaboration that the phasing out of animal procedures will require.
Working within these constraints, the NCad will do its utmost to be able to submit a clear opinion in October 2016 that sets out concrete goals and necessary steps for phasing out animal procedures. To that end, the NCad will explore which avenues are likely and which are not likely to offer opportunities, and determine which steps are necessary to phase out animal procedures in specific sectors.

Given the breadth of the field in which animals are used for scientific research and the specific objectives and approaches involved, the NCad will need to prioritise its action plan to some degree. In the view of the NCad, any elaboration of the request should therefore first identify the most promising sectors in the medium term. The objectives of current animal procedures in these sectors must be examined closely to establish the reason for these procedures and identify any alternatives that do not involve animal procedures, but which still serve these objectives considered. Animal procedures required by law may be used as an example. The quality and risk models underlying these procedures will be analysed, as these may offer guideposts for a new, non-animal strategy.

The NCad will be working intensively with the National Institute of Public Health and Environmental Protection (RIVM) on the scientific and legal aspects of the strategy. Furthermore, multiple national and international scientific institutions and regulatory organisations and authorities will be consulted.
With respect to the strategy's social and policy aspects, and further to the reports and documents referred to in the request for advice, civil-society organisations and foundations in particular will also be involved, notably the Dutch Society for the Replacement of Animal Testing and Eurogroup for Animals: their perspectives, suggestions and recommendations will demonstrably contribute to the opinion.

Discussions have since taken place with ZonMw (The Netherlands Organisation for Health Research and Development) and the Dutch Society for the Replacement of Animal Testing and these parties have indicated their willingness to act as a

sounding board for the NCad and put forward suggestions. However, they view their role as relatively limited, given their other priorities.
While the RIVM is certainly willing to do what it can, its available capacity is limited. I therefore ask that you request the RIVM to prioritise its efforts to assist in responding to this request for advice.

In drawing up its advice, the NCad will certainly consider transition thinking. Furthermore, the NCad is aware that for radical changes to current animal procedure practices (i.e. the phasing out of animal procedures) to succeed, much will depend on the possibilities for safeguarding and/or recalibrating the original societal objectives (such as health, safety and disease control) behind animal procedures.

By autumn, the NCad expects to be able to issue an opinion in outline regarding the transition process (phase-out of animal procedures in prioritised sectors in 10 – 15 years).
The NCad wishes to emphasise in advance that achieving a future that is free of animal procedures will require significant efforts, domestically and especially internationally, from all organisations involved.

After all, previous experiences have taught us that much time is lost between technical innovations and their eventual acceptance/implementation, and that the biggest challenges are not necessarily of a scientific nature.

I assume that you are in agreement with the strategy outlined in this letter."

The Minister for Agriculture's ambitions are in line with the NCad's efforts to achieve a substantial reduction in the use of laboratory animals wherever possible, in combination with an improvement in the scientific output and quality of research. The NCad makes recommendations for accelerating the transition from animal procedures to innovative non-animal researchs.

In order to respond to the request for an opinion, the NCad carried out a narrative review, using both reports and articles and up-to-date reporting in the press and social media. In addition to the parties suggested by the Minister for Agriculture and the NCad, a large number of experts were consulted (see page 75). During the course of the activities, there was regular contact with the Think Tank, ZonMw and the Dutch Society for the Replacement of Animal Testing, which are investigating the funding options for innovation without laboratory animals as part of a parallel project.

On 9 June and 7 July, the NCad organised workshops for experts on the opportunities for innovation without laboratory animals in the fields of regulatory and fundamental and translational research respectively. Appendix 4 contains a description of these meetings. The RIVM was actively involved in these workshops and in their organisation.

In addition, in the context of this request for an opinion, the NCad set up a discussion group within the professional networking application LinkedIn: "Towards a future of scientific progress without the use of experimental animals"[9] and, by 17 November 2016, the group had 245 members. Stakeholders were also invited to provide input through NCad's own website and social media. This input is contained in Appendix 5.

On 8 September 2016, a public consultation on this request for an opinion took place in The Hague. An overview of the participants and the outcome of this consultation can be found in Appendix 6.

3. Opinion

Over the course of the years, a great many reports have been written on how to ensure implementation of the 3Rs and a reduction in the use of animals in research (see Appendix 3). It is clear that many of these reports have not been properly followed up. In each case, the government recognises the importance of the recommendations and takes some of them on board, but fails to take adequate concrete follow-up measures, perhaps for budgetary reasons. As a result, many initiatives do gradually make progress, but not at the rate that is possible and societally desirable. The NCad believes that it is only with a broad-ranging and coordinated effort by the ministries involved and other stakeholders that significant progress can be made in reducing the use of animals in research. The choice of a clear direction, clear objectives and concrete steps is essential in this context, but emotions, social structures and other factors over which less influence can be wielded inevitably play a role, given the nature of transitions (see Appendices 1 and 2).

The NCad's advice relates to the use of animals in research in a broad sense, but also identifies areas where the potential for reduction can be considered to be more promising than others. In its initial response to the request for opinion, the NCad indicated that, over the next ten years, significant progress could be made in substantially reducing the use of animals in research. Based on further investigations and consultations, the NCad believes that significant progress can be made in some areas, while more time will be required in others. The question is whether the non-animal research that society desires can be achieved in the coming decades.

The NCad's recommendations are based on two observations:

1. Animal procedures have led to successes in the field of diseases and the health and safety of humans, animals and the environment, but have gone hand in hand with animal suffering, ranging from mild to substantial. In a number of research areas, the animal model has become the "golden standard". This paradigm is perpetuated, amongst other reasons, because the current scientific quality assessment system[10] is generally based on bibliometric criteria[11] and because journals impose requirements on authors – e.g. the validation of data obtained through the application of an innovation without laboratory animals, using animal data. Moreover, the use of animal procedures is stipulated in many (test) guidelines and laws. The expectation is that abandoning the dependence on animal procedures as the gold standard will allow societal and scientific issues to be approached in a different way, potentially without the use of laboratory animals. Alternative (3R) approaches to research are becoming increasingly common and, given current developments in technology, will increase in number and importance. A review of the conventional paradigm could form the basis for acceleration of the transition to non-animal research. But this paradigm will only be abandoned if the parties involved in the field find, in practice, that animal procedures can no longer be regarded as the "gold standard", or are no longer delivering the necessary results.
2. The transition to non-animal research cannot simply be achieved by making funding available for alternatives and innovation. The issue is far too complex for that. Although the focus is on replacement and reduction, the refinement of any animal procedures that are still regarded as necessary must also be actively

considered on a long-term basis. This can be done by encouraging research with regard to laboratory animals that focuses on minimising the suffering that they experience and optimising their welfare, for example.

The NCad's recommendations to the Minister for Agriculture are summarised below under three themes (Clear transition objectives, Transition Strategy and Management of the transition by the Ministry of Economic Affairs) and are justified in Section 4.

Clear transition objectives

1. In the field of ***regulatory safety research***, there are technical and strategic opportunities for completely phasing out animal procedures by 2025, whilst maintaining the existing level of protection. The NCad recommends for the Minister for Agriculture to adopt this clear policy objective and disseminate it on a national and international scale.
2. Within the field of ***fundamental scientific research***, the opportunities for a substantial reduction and phasing out of the use of animals vary from one area to another. The NCad recommends for the Minister for Agriculture to develop a ten-year vision for each area of fundamental scientific research in consultation with the public and the scientific community, with a view to reducing the use of laboratory animals, whilst maintaining the scientific objectives. This vision should inform the innovation strategy, which should systematically focus on the sharing of knowledge.
3. Within the fields of ***applied and translational research***, in which faster progress can be made, the NCad recommends for the Minister for Agriculture to encourage the exploitation and strengthening of these opportunities by focusing heavily on innovations without laboratory animals. By doing so, the Netherlands will be able to achieve its objective of becoming international leader in innovation without laboratory animals in the fields of applied and translational research by 2025.
4. By focusing on practices that do not involve laboratory animals and actively reflecting on the use of laboratory animals in education, the use of animals for ***education*** and training can be significantly reduced.

Transition strategy

The NCad offers the Minister for Agriculture the following recommendations:

5. Take the lead in calling for a new regulatory risk assessment procedure for substances at EU and international level, based on an intelligent and flexible step-by-step approach, without the use of or with minimum use of animal procedures.
6. Make the innovation policy of the Ministry of Economic Affairs more chain oriented and encourage multidisciplinary collaboration, so that promising innovations without laboratory animals can be better exploited and can progress more easily from development to application, potentially in a number of different areas of application.
7. Invest in the valorisation and acceptance of non-animal methods.
8. Ensure that better use is made of the results of research on human subjects.
9. Investigate risk acceptance in the field of regulatory research involving laboratory animals and invest in risk communication.
10. Ensure that monitoring and evaluation takes place and make knowledge concerning innovation without laboratory animals and 3R alternatives more available.

Management of the transition

The NCad offers the Minister for Agriculture the following recommendations:

11. Based on the Ministry of Economic Affairs' guiding role in the process, also involve other relevant ministries, in order to ensure that a consistent and coherent policy is developed at national level.
12. Ensure that all national stakeholders jointly establish an Agenda for Innovation Without Laboratory Animals and include it in a new route to be set up within the National Science Agenda.
13. Ensure that its guiding role benefits from an effective organisational structure.
14. Use the leading role of the Netherlands to accelerate the transition at international level as well.

Given the importance of this matter to society, in order to accelerate a further substantial reduction in the use of animals in research, without losing sight of scientific objectives, the government must set clear goals, define an interdepartmental transition strategy and play a guiding role in the process.

4. Substantiation of the opinion

The opinion is substantiated using the same three themes as are used in the recommendations: Clear transition objectives, Transition strategy and Management of the transition. Where relevant, a distinction is made between regulatory research, fundamental scientific research, applied and translational research and education.

4.1 Clear transition objectives

Transition to non-animal research in all fields of research involving the use of animals, whilst maintaining the existing level of protection and research objectives, cannot be achieved in full over the next ten years. According to the NCad, there must be a move away from existing ways of thinking and practices over this period in a number of fields, and this can definitely be achieved. In areas where there is potential for a reduction in the use of animals, or where there will be within the next few years, there will need to be a paradigm shift away from treating "animal procedures as the gold standard".

During one of the workshops organised by the NCad, the development of innovative research methods was described as follows: "The Netherlands is extremely 3R minded, but the initiatives are fragmented. The question that must be asked is when and where there is a need to go beyond simply facilitating innovation." So far, the existing scientific, economic and social potential of innovations without laboratory animals has not been used in a sufficiently targeted way to promote and, where possible, accelerate the transition to non-animal research methods.

The NCad therefore recommends for the Minister for Agriculture to formulate clear objectives for the transition to non-animal research methods and disseminate these objectives on a national and international scale. With political and financial support, targeted policy objectives of this nature, which are preferably quantifiable, can act as a catalyst in the transition process. In public discussions, it is regularly suggested that a clear objective could be to no longer accept certain animal procedures, such as those involved in research into certain lifestyle-related conditions and research designed to increase the productivity of farm animals in intensive cattle farming.

The NCad believes that the objectives below are both ambitious and realistically achievable, provided that the national and international effort described in the following sections is invested.

The use of laboratory animals in regulatory safety testing of chemicals, food ingredients, pesticides and (veterinary) medicines can be phased out by 2025, whilst maintaining the existing safety level

The emergence of innovative technologies[12] that can be applied to cellular and tissue biology play a key role in the increased understanding of the mechanisms of action of substances and can completely replace animal procedures[13]. If, in addition, there is a radical change in the test strategy[14], i.e. to one that is based more on exposure and on knowledge of kinetics and molecular biology, the unnecessary use of animals can be reduced and the relevance of the research increased. The NCad also believes that this paradigm shift would deliver at least an equivalent, but very likely a more reliable, risk assessment. At this stage, however, due to the complex composition of these products and generally complex mechanism of action, the regulatory

pre-clinical research associated with the registration of new biologicals (such as a vaccine or monoclonal antibody) cannot be phased out at the same pace.

The use of laboratory animals in regulatory tests for the release of biological products, such as vaccines, will be phased out by 2025, whilst maintaining the existing safety level

Physicochemical and immunochemical techniques[15] for the characterisation of substances in particular, but also innovative techniques in the field of tissue culture, can help avoid the use of animal procedures[16]. As was presented in its opinion on procedures involving cats and dogs, the NCad believes that vaccines that have already been tested for registration for market acceptance and for which the batches are produced in a consistent manner, should not have to be tested again for batch release using animal procedures.

Within the field of fundamental scientific research, the reduction or phasing out of the use of animals is not realistic in the short term in all areas of research

The potential for acceleration of the transition varies from one area of fundamental scientific research[17] to another, and in several of these areas a significant reduction in the use of animals as a research model (paradigm shift) is regarded as not yet possible or even harmful.

Fundamental scientific research is, by definition, the area where fundamental knowledge is acquired concerning the workings of complex biological systems. In a number of areas of fundamental research, it is anticipated that researching of the entire organism would be difficult to replace at this stage[18]. Moreover, it is not possible to predict in advance what direction scientific questions will take and whether it will be possible to answer them using innovations without laboratory animals or other approaches. At the same time, the NCad has already drawn attention to the fact[19] that the availability of new technologies such as CRISPR-Cas may even facilitate the use of laboratory animals by enabling more targeted work on fundamental issues.

The NCad is convinced that many people working in the field will continue to strive towards the use of non-animal methods and approaches, particularly if they lead to better knowledge. The ethical assessment by the CCD of project proposals that involve animal procedures will also move things further in this direction. Nevertheless, the NCad notes, from the workshops in particular, that knowledge of the development of innovations and approaches without laboratory animals is not always widely known and shared in the various different disciplines. The systematic application of Synthesis of Evidence may improve matters in this respect, as may the promotion of multidisciplinary collaboration in the problem analysis phase.

The NCad recommends that in the field of fundamental scientific research, visionsvision are drawn up for each discipline or cluster of disciplines that can serve as a basis for the sharing of knowledge and further knowledge development. These visions can also be used to justify fundamental scientific research to the public and any essential use of laboratory animals that this may entail. In order to guarantee support, it is essential in this context that these visions are developed by the pioneers within the relevant field, in consultation with patient and animal welfare organisations and transition experts.

Each vision must contain clear transition objectives for the next ten years, with a view to achieving non-animal research that is consistent with the core focus of the relevant scientific research area. They must also provide insight into the potential[20] of the field concerned, the innovations without laboratory animals that could enable this potential to be achieved and how these aspects will be included in education and training in this field. The visions will form part of the Agenda for Innovation Without Laboratory Animals that the NCad has recommended, as explained in more detail below (see page 27).

This will allow the Netherlands to have clear ambitions with regard to working without the use of animal procedures in the field of fundamental research, but will, at the same time, ensure that it does not isolate itself from the international community. And it will also provide greater insight into innovation without laboratory animals and 3R research and application in the field of fundamental scientific research. This ties in with the NCad's previous recommendation to make more data available on the use of animals in research.

The Netherlands will be an international leader in the field of innovation without laboratory animals in applied and translational research by 2025

In the field of applied and translational research[21], progress could be faster than it is at the moment, because this field in particular has innovative potential that could be better deployed and exploited. The NCad recommends for the Minister for Agriculture, in order to exploit and reinforce these opportunities, to focus heavily on innovations without laboratory animals, amongst others in the field of the development of human models for human diseases. To this end, more attention must be paid to the chain from "incubator" to "actual implementation" and to alternative approaches to risk. The promotion of cross-sectoral and multidisciplinary collaboration must form part of the innovation policy. Naturally, all the other recommendations in this opinion contribute to the Netherlands' ambition of being an international leader in this field.

By focusing on animal-free practices and actively reflecting on the use of laboratory animals in education, the use of laboratory animals for education and training can be significantly reduced

The NCad believes that it is desirable to significantly reduce the use of animals in education. In its advisory report "Procedures involving cats and dogs" *("Proeven met honden en katten")*, it therefore recommended phasing out the use of cats and dogs in paraveterinary courses. The NCad also sees potential for animal-free education in other biomedical courses.
In doing so, it draws attention to the many alternative teaching models available and to the need to encourage critical and ethical reflection of the use of animals in education in young professionals. Teaching a new generation of professionals involved in biomedical research without the use of animals may trigger the paradigm shift that is required. In veterinary science also, non-animal models are being used increasingly often. Teaching completely without the use of laboratory animals, however, will not be possible, because clinical animals (animal patients) are also registered as laboratory animals.

In order to accelerate the transition to animal-free education, the NCad recommends including this field in the Agenda for Innovation Without Laboratory Animals as well.

In order to ensure that the animal procedures that are still required are implemented in as refined a way as possible, adequate initial and refresher training is essential. Although animal procedures will continue to be necessary in the final phase of training at this stage, efforts to encourage a non-animal mindset amongst students should continue.

4.2 Transition strategy

Research on a research model of the same species as the target animal, including humans, is preferable to that on a research model of a different species, provided that it is safe and responsible and complies with the principles of the 3Rs. Innovations without laboratory animals include:

- methods that make it possible, taking into account ethical, technical, methodological and statistical constraints, to take measurements directly from humans (e.g. smart devices and micro-dosing);
- technologies that are based on human material or material from the target animal (e.g. organs-on-chips and organoids); or
- technologies that provide useful information without additional animal procedures having to be carried out (e.g. computer simulations, data mining and tissue banks containing human material).

The application of technological developments could also make it possible to delay the use of laboratory animals until as late as possible in the development process of a drug or therapy.

By promoting innovations without laboratory animals and exploiting them to the full, the use of laboratory animals can be reduced. In this section, the NCad describes a strategy for accelerating the transition to non-animal research methods.

Work at the international level to obtain a revision of the regulatory risk assessment process

In order to guarantee the safety of substances, animal procedures are legally required or recommended at EU and international level[23]. Risk assessment in this context focuses primarily on the hazard of the substance. In many cases, the justification for the prescribed animal procedures is based more on historical than on scientific grounds.

As a result of the progress made in scientific toxicological research and the significant increase in our understanding of molecular biology a movement[24] that focuses on innovations for a new approach to the risk assessment process and risk policy has emerged at international level in recent years. Our understanding of the mechanisms of action of substances in humans and animals is increasing, and this will enable a new and more accurate approach to the risk assessment of substances: a radically different approach to risk assessment that is based more on exposure and knowledge of kinetics and pharmacodynamics (through a combination of in vitro, in silico and ex-vivo test methods, supplemented by and corroborated by historical data) than on hazards. In this new approach, the unnecessary use of laboratory animals can be phased out and the relevance of the research can be increased. The basic principle here is that the current level of protection for humans, animals and the environment is maintained.

This new approach to risk assessment will not be possible without reference to available cumulative historical data from animal procedures, data on the physicochemical properties of materials and 3R data. The quality, scope and accessibility of such datasets is therefore key to the reliability of innovative risk assessment that does not involve animals.

The NCad recommends for the Minister for Agriculture to strive for a review of the existing risk assessment process. The alternative approach to risk assessment outlined above can be implemented as a step-by-step approach. Initially, the design can be tailored to the intended purpose (e.g. the safety of the unborn child or the safety of the central nervous system). As a temporary hybrid situation, the innovative prediction models that are already available can be used alongside the animal models that are still being used (parallel testing). The NCad anticipates that the ongoing development of adequate prediction models such as tissue and organ models on intelligent microplates (organs-on-chips), 3-dimensional mega QSAR read across, meta-analyses and a growing understanding of system biology will result in a further increase in our understanding of the mechanisms of action of substances in humans and animals. This will enable high-quality risk assessment of substances, which will make animal models superfluous. Most of these advanced prediction models are being developed in the US, but similar innovations are also being developed in Europe and the Netherlands.

Given the international nature of this area of research and the regulations involved, the above-described new approach to risk assessment can only be achieved through significant international collaboration and acceptance by the regulatory authorities. The Netherlands cannot achieve it on its own. Coordinated efforts are required at EU and international level.

In addition, the NCad believes that it is important that risk models that aim to protect humans and animals are systematically and periodically reviewed in relation to the availability of innovations without laboratory animals.

Make the Ministry of Economic Affairs' innovation policy more chain oriented; promote multidisciplinary collaboration

The route from "incubator" of promising innovations to acceptance and application in practice is littered not only with obstacles but also with opportunities for acceleration. In most cases, current grants for innovations cover only a small part of this route (mainly the early part). The NCad believes that a more chain-oriented innovation policy would result in better utilisation of promising innovations without laboratory animals and easier progression from development to application, potentially in several fields of application.

By better aligning grant structures, so that researchers or innovation entrepreneurs can also obtain funding for the distribution and commercialisation phase once they have developed their innovation, the "valley of death", that until now has primarily been defied by a combination of chance, focus and a strong desire, can be bridged. The fund recommended by the Think Tank could also be used for investments in validation and valorisation projects.

In a chain-oriented innovation policy, the involvement of governments, assessment authorities and (end) users as early as possible in the development process of an innovation is a critical factor for success. Cross-sectoral and multidisciplinary collaboration will be required in this context and must therefore be promoted. By setting clear objectives such as innovation without laboratory animals as a core theme, the government policy will create clarity and the various stakeholders should not work against each other.

When obtaining funding for science and innovation, public-private partnerships could be more effectively promoted (financially if possible), with any such partnerships enabling the parties involved to mutually agree on how the funds and intellectual property will be divided. In addition, it can be made possible for private organisations (within the constraints of state aid rules) to be able to apply for funding for innovation without laboratory animals under more innovation programmes than they can at the moment, thereby accelerating the transition.

By assessing an innovation at the outset, followed by interim reviews, it can be evaluated whether the innovation actually has sufficient potential to progress within the chain, and which barriers will need to be eliminated to enable it to do so. In this context, consideration could be given to the use of Technology Readiness Levels (TRL) to assess the potential or importance of an innovation, as is done in the EU's Horizon 2020 programme.

Invest in the valorisation of non-animal methods

Every developed non-animal method must be validated in order to ensure that it can be accepted as an alternative by the industry and, where appropriate, by the regulatory authorities and can be implemented in the various directives. In the case of regulatory research on biological products, the Biological Standardisation Programme (BSP), for example, performs such interlaboratory validation studies in collaboration with the European Pharmacopoeia. The European validation lab EURL-ECVAM[25] has set up a Network of Validation Centres (NETVAL) in pursuance of Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. In the Netherlands, the research institutes RIKILT and TNO (Netherlands Organisation for Applied Scientific Research) are the EURL-ECVAM NETVAL laboratories.

The NCad recommends for the Minister for Agriculture to promote the validation of non-animal methods by ensuring, in accordance with the provisions of the Directive, that the Netherlands actively provides input to the European Commission with regard to the establishment of the priorities for validation studies. The willingness of Dutch laboratories to participate in validation studies could also be stimulated.

Innovative methods are often directly related to data and materials of human origin, and a comparison with the human patient would therefore be a logical comparison for validation purposes. This is in contrast to conventional validation, where data from animal studies is often used. If no human data is available, it could be created in studies that run parallel to the established drug development process.

At the request of the Minister for Agriculture, the National Institute of Public Health and Environmental Protection (RIVM) and the Medicines Evaluation Board (CBG) should be able to instigate a review of the validation procedure for chemicals and medicine, which would enable the Netherlands to play a pioneering role in Europe. Efforts could then be made to achieve a validation process at European level (and possibly also internationally through OECD, ECVAM, ICCVAM and JACVAM) that is accurate and, at the same time, faster and more straightforward.

In regulatory clinical research, medicines that were successful in animal procedures often fail in clinical trials. For these instances, so-called backward validation studies can be used to investigate or determine the predictive value of pre-clinical animal tests and innovative methods for clinical research on human subjects. On the basis of the insights obtained, pre-clinical research models can be improved. The NCad recommends for the Minister for Agriculture to make funds available for this.

Ensure that better use is made of the results of research on human subjects

In some areas of research, more use could be made of data from human research or more data could be obtained from human research (e.g. through the use of micro-sampling or micro-dosing, tissue banks, patient information, epidemiological data, screening and Synthesis of Evidence).

This ties in with the movement within biomedical research towards precision- and personalised medicine. If developments continue at the current rate, it is not inconceivable that organs-on-chips could be refined into human-on-chips within 50 years, which would enable animal procedures to be reduced, or even replaced. In addition, the development of organoid cultures offers excellent opportunities for regenerative medicine, which is also one of the routes in the National Science Agenda.

Moreover, informed patients and healthy citizens could make an even greater contribution than they do at present by making bodily material available (in the context of a surgical intervention) or by participating in research themselves as subjects, for example. Consideration should be given to how this can be encouraged and what research can be safely and meaningfully conducted in humans, whilst respecting their privacy. Effective solutions must also be developed with regard to costs, complexity, logistics and communication.

For many patient organisations, the current development period for medicine is too long. They are calling for a faster licensing period. It is not possible to predict whether the paradigm shift proposed by the NCad in the field of regulatory research will be sufficient to achieve this acceleration of the licensing period that society desires. The intelligent, step-by-step approach will, however, make it possible to select promising substances or treatments at an earlier stage.

Under certain conditions, it should be easier to apply new treatments to human subjects. Unnecessary legal obstacles to this would have to be removed. This requires transparency with regard to risks and full freedom of choice of the subject or patient concerned. The potential that this offers should be investigated further by a designated party, and involving organisations such as the CCMO (Central Committee on Research involving Human Subjects), RIVM and TNO is also recommended.

Investigate risk acceptance in the field of regulatory research and invest in risk communication

The effective protection of the health of people and animals will benefit from taking a modern approach to risk management which, whilst respecting old traditions and conventions, makes full use of innovative techniques and new approaches to risk that are consistent with the requirements of society.

Risk assessments will be based on the increase in scientific knowledge concerning biological processes, disease processes and exposure scenarios supported by innovations without laboratory animals. Depending on the field, the development of innovations without laboratory animals will result in a level of health protection that is accepted by society, but with fewer procedures involving laboratory animals.

For safety and efficacy research in particular, the extent to which society and assessment authorities are willing to accept risks on behalf of society plays a role.
Citizens must be able to trust the assessment authorities (i.e. the government) to ensure that they are protected against unacceptable risks.

When determining the approach to be taken in respect of the necessary risk communication, it is recommended that a designated party be commissioned to further investigate the perception of risk and risk acceptance amongst assessment authorities, citizens and patients from a psycho-social perspective.

Ensure that monitoring and evaluation takes place and make knowledge concerning innovation without laboratory animals and 3R alternatives more available

In a complex transition issue such as that of the use of animals in research, it is crucial to monitor and evaluate which interventions have been successful and which have not, and where adjustment is possible and advisable in order to allow the intervention to have a broader application or greater impact. Consequently, the NCad recommends for the Minister for Agriculture to make a priority of monitoring and evaluation of the progress made in reducing use for regulatory purposes, defining visions within fundamental scientific research and, wherever possible, phasing out the use of laboratory animals in biomedical education, and to use the data warehouse for animal procedures and 3Rs recommended previously by the NCad to disseminate this information[26].

In the interests of access to knowledge, when European Directive 2010/63/EU is reviewed in 2017, efforts should be made at European level to achieve greater transparency with regard to the use of laboratory animals in research. If research data concerning innovations without laboratory animals (e.g. available cumulative historical data from animal procedures, the physicochemical properties of substances and 3R data) is to be effectively shared, linked and evaluated through Synthesis of Evidence, it is essential that access to 3R knowledge is improved and made centrally available to researchers. The NCad therefore recommends creating the data warehouse on animal procedures and 3Rs as quickly as possible and promoting at EU level with a view to interconnecting similar data systems in the EU. ECVAM could play a coordinating role in the optimisation of a European database, but the European Partnership for Alternative Approaches to Animal Testing (EPAA)[27], the European link between policy and industry, should also be a key player in collaboration in this context.

The NCad also believes that it would be sensible to investigate the possibility of creating an Innovations Without Laboratory Animals Index in collaboration with EU Member States, along the lines of the Access to Medicine Index[28]. DThis could help raise the profile of the work that is being undertaken in the field of innovation without laboratory animals and act as a source of inspiration for those involved in the field of research involving animals.

4.3 Management of the transition

Although there are already a large number of initiatives that focus on innovation and 3R development and application, the transition to non-animal research will not happen by itself. The existing 3R initiatives and innovation pathways can be given additional momentum or accelerated through management and focus, both within the Netherlands and internationally. International collaboration is key, within the government, within risk assessment and within fundamental scientific research.

Based on the Ministry of Economic Affairs' guiding role in the process, also involve other relevant ministries

Responsibility for "animal procedures" in the Netherlands lies with the Ministry of Economic Affairs, but animal procedures also take place within the policy areas of other ministries (Education, Culture and Science, Health, Welfare and Sport, Defence, and Infrastructure and Environment). These ministries each have their own policy and run their own grant systems.

Since the use of animals in research is a complex issue in which a wide range of parties play a role and much must be achieved at international level, efforts to accelerate the transition process must be intensively managed, starting with prioritised research areas and then going further. The efforts of all the players involved on the various levels must be coordinated, and ideas, strengths and stakeholders must be combined. The government is the only party that can take on this overarching management role. The NCad therefore recommends for the Minister for Agriculture to assume this management role and embed it for a number of years.
Furthermore, the NCad recommends for the Minister for Agriculture, when undertaking the proposed review of the Experiments on Animals Act in 2019, to take into account:

- that the Central Authority for Scientific Procedures on Animals (CCD) may impose conditions regarding the use of new non-animal innovative techniques while a project is running. The review should consider how research practice has approached these requirements;
- how visions, transition objectives and the Agenda for Innovation Without Laboratory Animals have played a role or could play a role in project assessment;
- the monitoring of progress in the field of innovations without laboratory animals and 3Rs;
- the link with the European field and the extent to which European and international support has been obtained for the Dutch ambitions with regard to animal-free research.

From Interdepartmental Working Group on Alternatives to Animal Testing to Interdepartmental Management Group

Clear interdepartmental cooperation is also crucial. Transforming the existing Interdepartmental Working Group on Alternatives to Animal Testing (IWAD) into an Interdepartmental Management Group (IR) will ensure that actions are consistent, effective and collaborative. By collaborating in this way, policy on animal procedures can be linked to related policy issues, such as the development, assessment and registration of (veterinary) medicines, environmental legislation and science policy, along the lines of the antibiotics debate and the One Health[29] approach. That way, links with related (policy) issues that could accelerate the desired transition, such as sustainability and

investment schemes, corporate social responsibility (CSR) and the business model of disruptive technologies and innovations, can be actively investigated. In this context, it is important that innovations without laboratory animals are embedded not only locally but also in the mainstream of the various policy fields, so that progress in the various fields is mutually reinforcing and policy plans in this area are not at odds with each other.

Link innovation policy to Top Sector policy

The NCad also recommends a joint approach to the realisation of the policy on innovation and the policy on so-called Top Sectors with regard to the achievement of non-animal practices. Making the principle of the 3Rs an explicit part of the Top Sector policy will accelerate the development and application of innovations without laboratory animals in a number of different fields.

This joint approach should consider the following:

- the development and further optimisation of the collaboration within and between the public and private sectors;
- the promotion of opportunities in the field of big data management in relation to the undertaking of risk assessments;
- the coordination of the promotion of innovations without laboratory animals and developments in all relevant international and EU bodies, including the overarching national and international assessment authorities;
- joint policy on education and training in the field of innovation without laboratory animals, and the 3Rs;
- promotion of the development and application of new approaches to risk assessment and management;
- the development and implementation of positive incentives that contribute to the development and application of non-animal research methods, such as:
  - tax breaks for investments that support the transition;
  - a longer data protection period for companies that use non-animal methods and/or accelerated licensing procedures;
  - accelerated incorporation of patented and non-patented innovative methods in the regulations.

The NCad endorses the Think Tank's recommendation of setting up a fund for the development and use of innovations without laboratory animals. This fund will be directed at the entire knowledge and innovation chain and, as a result, will act as a link between different scientific programmes within NWO (The Netherlands Organisation for Scientific Research), the technology foundation STW and ZonMw (The Netherlands Organisation for Health Research and Development), as well as the programmes run by and knowledge issues addressed by, amongst others, TNO, the Institute for Translational Vaccinology (IntraVacc) and the RIVM in this field and related themes.
The NCad also recommends seeking collaboration with initiatives that are designed to support science and innovation, such as the NL Next Level project, a collaboration between the Confederation of Netherlands Industry and Employers (VNO-NCW), the entrepreneurs' association MKB-Nederland, the Dutch Federation of Agricultural and Horticultural Organisations (LTO Nederland) and the knowledge sector. In this context, the NCad recommends for the Minister for Agriculture to also collaborate with NC3Rs in the UK, BfR in Germany and similar bodies in other Member States.

Ensure that all national stakeholders jointly establish an Agenda for Innovation Without Laboratory Animals and include it in a new route to be set up within the National Science Agenda;

The NCad recommends for the Minister for Agriculture, with the involvement of the Interdepartmental Management Group, to investigate the possibility of setting up an additional route within the National Science Agenda: the Agenda for Innovation Without Laboratory Animals. The visions for fundamental scientific research, together with the transition objectives of the other areas of research, will form part of this Agenda for Innovation Without Laboratory Animals.

The next step in the Agenda for Innovation Without Laboratory Animals, which will constitute the joint approach to be adopted by all national stakeholders that play a role within the relevant policy areas, including business and industry and societal organisations, must not simply be a joint declaration of intent or a broad list of general agreements. The NCad recommends concluding an agreement containing specific ambitious but achievable objectives[30], with a distinction being made between the various fields of research and the clear transition objectives agreed for them.

In this same context, the NCad recommends for the Minister for Agriculture to urge the research community to undertake further national and international multidisciplinary collaboration and to facilitate this through assistance under the incentive programmes earmarked for this purpose, such as ZonMw's More Knowledge with Fewer Animals (MKMD), the fund recommended in the Think Tank's report and the Top Sector Health and Life Science.

Ensure that the guiding role benefits from an effective organisational structure

If the Interdepartmental Management Group is to be able to manage, monitor and implement the Agenda for Innovation Without Laboratory Animals effectively, it will require a supporting body, an organisational structure that is properly equipped to bring the various parties together and that has the status and mandate to initiate and support the necessary activities. In this context, it is important to ensure that different initiatives and powers converge, including the project office that will be set up on the basis of the Think Tank report, the generation of funding and public-private initiatives. The NCad recommends considering a number of different types of organisational structures for this joint approach, such as, for example, that of the NC3Rs in the UK, the BfR in Germany and similar bodies in other EU Member States.

Use the leading role of the Netherlands to accelerate the transition at international level also

The NCad endorses the Think Tank's statement that the Netherlands is in "a unique position to promote itself at international level as a leader in the field of *innovations without laboratory animals:* internationally renowned knowledge institutions, a wealth of innovative businesses, a growing public desire for sustainability and a culture that encourages interaction and dialogue between stakeholders."
In collaboration with other countries and organisations, the Netherlands can exploit this position to accelerate the use of non-animal methods through innovations without laboratory animals at international level too.

In the context of the desired transition and the recommended clear transition objectives, the Minister for Agriculture can take the following action in an international context:

- Urge the European Commission to define a European strategy that takes an ambitious and integrated approach to non-animal research, one that includes animal welfare and the 3Rs in impact assessments and the development of new legislation and regulations. Also, call for existing legislation and regulations to be critically reviewed in this respect, and for it to be mandatory for accepted alternatives to be included, for funds to be made available for the further development of innovations without laboratory animals and for EU standards to be observed in commercial treaties.
- In collaboration with the ministries of Health, Welfare and Sport and Infrastructure and the Environment, call for a regulatory risk assessment process that is based on an intelligent and flexible step-by-step approach, with minimum use of animals, and enter into international collaborations in this context. More specifically, consider collaborating with the US organisations EPA (for the risk assessment of substances and pesticides) and FDA (for the risk assessment of medicines and food additives), as part of a European alliance or otherwise, on the theme of New Risk Management in approval of substances.
- Urge assessment authorities to facilitate or be enabled to facilitate so-called safe harbours that enable experimentation with promising innovations without laboratory animals in the science-driven development of medicine, just like the FDA facilitates safe harbours that are used in a slightly different way for the development of gene and cell therapies. This would allow the potential of innovative ideas that have not yet been validated to be explored and compared in parallel to the standard test processes in a safe environment, without the intervention of legislation and regulations, but still with a view to actual application within the regulatory system. Scientists can work on the further development of innovations with a view to application and, at the same time, the assessment authorities can gather insight into and gain confidence in the innovative methods concerned. This will encourage the implementation and ultimate acceptance of promising innovations in regulatory research.
- In collaboration with the ministries of Health, Welfare and Sport and Infrastructure and the Environment, the RIVM and relevant international organisations, endeavour to obtain European agreements that make it easier to depart from regulatory animal procedures where possible through the use of validated alternative methods. Also, aim for transparent communication regarding situations where alternatives to the regulatory animal procedures have been used. In current regulatory research, animal procedures are performed in accordance with internationally accepted test guidelines issued by the European Commission, OECD, ICH and VICH, for example. These guidelines formally provide scope for modifications and even for a regulatory animal test not to be performed. However, any such modification must be justified in detail and may delay the evaluation of the case. Consequently, parties submitting a case for licensing of a substance rarely make use of this option.
- In this same context, advocate the removal of test guidelines once accepted non-animal alternatives are available and the rejection (omission from the formal case) of and imposition of a fine on test results originating from animal procedures for which an

internationally accepted alternative method is available. Despite the availability of accepted 3R test methods, conventional animal procedures are still being performed, and the results from these procedures are still being accepted by the assessment authorities. This should be regarded as a violation of Article 13.1 of EU Directive 2010/63/EU, and it is therefore recommended that this issue be discussed when this Directive is reviewed.

- Strive for better international harmonisation of test guidelines. In this context, make use of overviews by bodies involved in the validation, implementation and regulatory acceptance of 3R alternatives, such as that drawn up for chemicals by the RIVM, and involve the Dutch representatives to these bodies in the process, e.g. OECD, the International Conference on Harmonization (ICH), the Veterinary International Conference on Harmonization (VICH), the WHO and the World Organisation for Animal Health (OIE). Endeavour to ensure also that new test guidelines cannot be introduced until an expert group has checked them in terms of the potential innovation without laboratory animals.
- Proactively contribute, through the Interdepartmental Management Group, to the programming of conferences where innovation without laboratory animals is the theme or one of the themes (e.g. The World Congress on Alternatives and Animal Use in the Life Sciences), in order to raise the profile of the topic of innovation without laboratory animals internationally and keep it in the public eye.
- Endeavour to ensure that the new European Animal Welfare Platform and the future European Animal Welfare reference centres address the issue of "laboratory animals" and that a working group on innovations without laboratory animals is set up.

5. Appendices

Appendix 1: *The Multi-Level Perspective (MLP)*

Transitions

Transitions are major, radical changes. They are far-reaching change processes in which both existing structures and practices and existing thought processes are gradually replaced by new ones. Social transitions can be defined as a permanent switch by a specific social system to a different culture, structure and practices. Van der Hoeven (2010) maintains that social transitions are the result of connected change processes in all parts of society, e.g. the economy, legislation and regulations and technology. Geels (2014) believes that transitions are the answer to persistent social problems, which can only be tackled by transforming the social system.

Change in itself is nothing unusual – society is constantly evolving, looking for innovations, new technological developments and new solutions to existing problems. What makes transitions different is the fact that they involve structural social changes at all levels of society, and often focus on greater sustainability.

Transition science is the perfect tool for analysing so-called wicked problems. Wicked problems are complex in nature: there is no simple solution to them, they do not have an obvious cause and it is unclear who is responsible for them. They involve a large number of players, all of whom have their own interests and perspectives for action. Wicked problems, such as the use of laboratory animals in research, are often deeply embedded in social structures and, consequently, are not easy to solve. If they are to be solved, the closely linked underlying structures must be changed. Geels (2014) maintains that wicked problems require transitions to new systems.

Multi-Level Perspective (MLP)

Transitions are often described and analysed with the help of the Multi-level Perspective (MLP). This conceptual model regards society, or the environment of the transition project, as a dynamic system comprising three levels: landscape, regime and niches.

Mapping the environment of the transition project may be relevant. This is because experience tells us that people often immerse themselves in their own innovation projects without taking the environment, the context, into account. And this context can be crucial to the success of the change process. The MLP maintains that all levels of this context – the landscape, the regime and the niches – are interrelated and affect each other (Geels, 2002).

Landscape

The landscape is the macro-level, which forms the broad context for the regime and the niches. It includes major social changes in the field of politics, culture and world views (e.g. globalisation and individualisation) or natural characteristics, which are difficult to influence and generally slow to change. The landscape can therefore

be regarded as the slowly evolving undercurrent of society. It incorporates the entrenched views on what is "normal" and "the way things are".

Regime

The regime is the meso-level, the structural layer that forms the context of common practices, rules and interests. It includes economic and political interests, routines, rules, knowledge and existing infrastructures. According to Geels (2014), existing regimes are bound by "path dependence". In other words, certain thought processes can make people "blind" to alternatives, and standard practices, values and views can thwart change.

Niches

The niches can be seen as the micro-level. They are protected from existing, dominant regimes, and therefore offer far greater scope for innovative developments. Within the niches, it is possible to depart from existing ideas, practices and customs, e.g. through new technologies.

The MLP is used to analyse transitions in terms of the interaction in developments between these levels. Between niche innovations and existing regimes in particular, a multidimensional struggle may ensue, in the context of a larger landscape trend. As can be seen from the model (see Figure 1), transitions occur as a result of developments in different "levels", which affect each other:

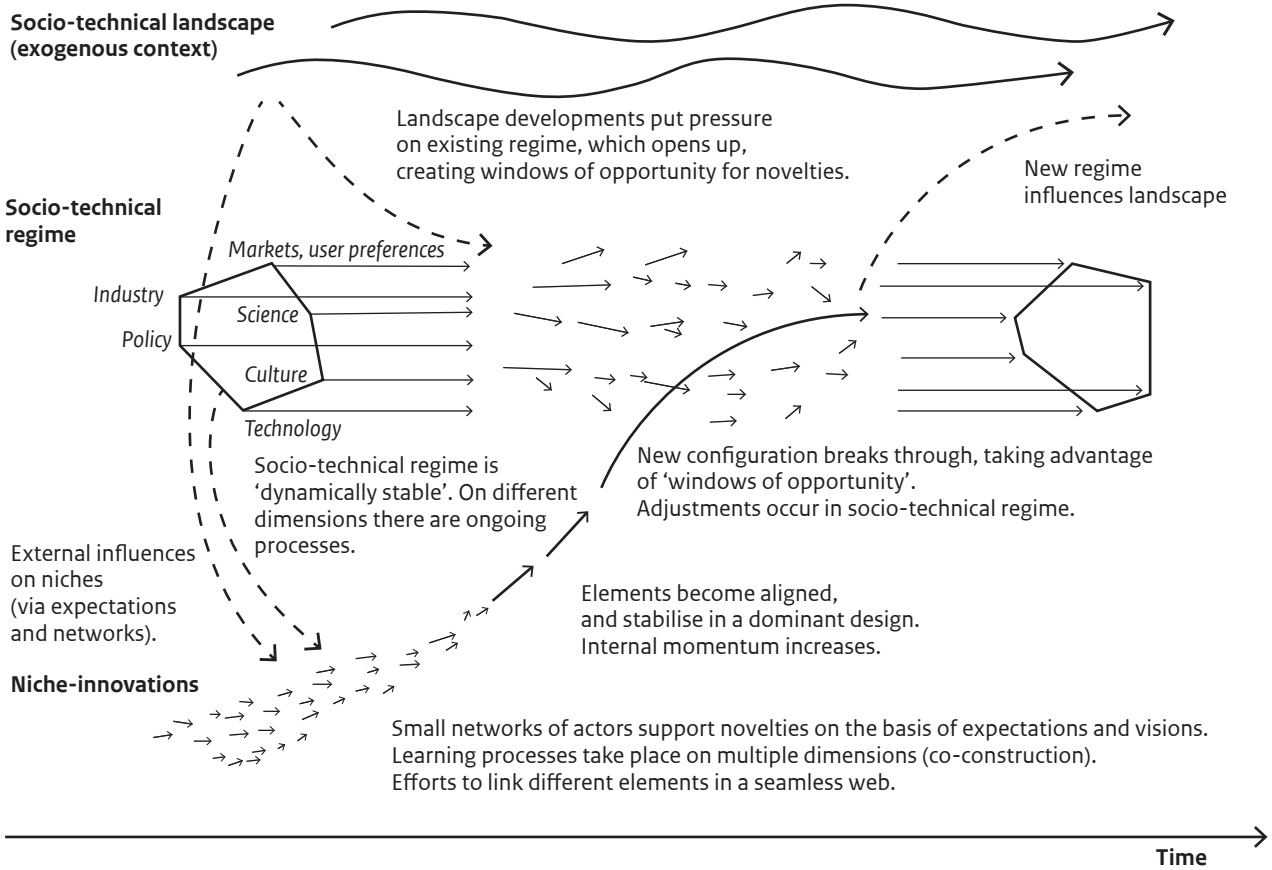

Figure 1: Dynamic multi-level perspective on transitions. (According to Geels, 2005)

So, transition processes are multi-causal and multi-level. In other words, they impact on niches, regimes and the landscape. Moreover, transitions are executed by many people (multi-actor) and go through a number of different stages (multi-phase). What is clear, however, from the figure, is that every innovation is initiated and takes shape within the niches. In the early phase, all manners of precarious processes are under way here around one or more new technologies. Developments in the niches are an essential part of the transition process, but are not sufficient to trigger a transition. The dynamics at landscape and regime level are also crucial in this context. At regime level, there must be a window of opportunity for the developments from the niches. This window of opportunity may arise as a result of developments at landscape level or developments within the regime itself, for example.

Changes and innovations can succeed if:

- there is sufficient pressure from the landscape on the regime;
- the regime can no longer solve existing problems and is therefore open, or more open, to change;
- sufficient innovations have been developed in niches and they are sufficiently robust.

In other words, innovations can only break out of the niches if they connect with ongoing dynamics at regime and landscape level. The overall transition process can therefore be regarded as the simultaneous occurrence and linking of multiple processes at different levels.

Why was MLP chosen as the tool in the workshops?

MLP was selected as the approach to be adopted for this request for opinion because it is ideally suited to analysing and understanding technological transitions in a social context, and it offers insights into how this transition can be managed.

The MLP offers a vocabulary for interpreting transition issues. This allows a neutral language to be applied to a politically sensitive issue, which enabled those attending the workshops to “understand” what others were saying.

Moreover, the MLP is a conceptual model that combines different developments and perspectives. It addresses not only technological factors but also political, economic and sociocultural factors. With a wicked problem such as the use of laboratory animals in research, it is crucial that these different perspectives on the problem can be taken into account, and the MLP provides the necessary scope for this.

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Appendix 2: *The context of the desired transition, seen from the Multi-level Perspective (MLP)*

Factors and movements within each of the levels (landscape, regime and niches) that impact on the use of laboratory animals in research are specified below using the MLP. As stated in the introduction, these factors and movements, in turn, form points of departure for activities that are designed to accelerate the transition to non-animal research methods.

Landscape

At landscape level, it is primarily political and social factors and movements that impact on the use of laboratory animals in research:

- Society's requirement for ***knowledge and development for health and safety*** of humans (and pets and livestock) is a key driver in the field of animal procedures. The growing demand for research into lifestyle-related conditions, ageing and related conditions, gender-specific conditions and new foods, for example, may result in an increase in the use of laboratory animals in research.
- Moreover, the demand for animal experiments is perpetuated by society's ***perception of risk,*** which is generally at odds with the actual risk, and the public's very limited inclination to accept negative effects and side effects (risks) of substances, medicines and vaccines. Departure from conventional research methods is also regarded as a risk.
- The need for safety-related research involving animal experiments has increased because previously fatal conditions are increasingly becoming chronic in nature. Consequently, greater attention must be paid to side effects and to side effects in ***specific target groups.*** For example, more and more new and existing treatments are becoming available for children. In many cases, the safety of these methods of treatment for children has yet to be determined.
- ***People increasingly want the freedom to make their own decisions*** and are demanding more of experts in terms of transparency, freedom of choice and social responsibility, for example. Patients are taking it upon themselves to obtain certain methods of treatment and are actively using social media in this context[31] (the facebook patient), as well as the opportunities offered by crowdfunding. The Internet, social media and fellow sufferers are increasingly becoming sources of knowledge, alongside the experts. If citizens and patients demand additional development and research in the field of medicines and treatments, these trends may result in the increased use of laboratory animals in research. At the same time, if citizens and patients were to call for better predictive testing and lend weight to this call by expressly requiring innovation without laboratory animals, a decrease in the use of animals in research might be the result. Especially if they help make this a reality themselves, by making bodily materials available and participating in research as a research subject, for example.
- There is strong public demand for ***new or better affordable medicines to be made available quickly.*** This is something that is expressly advocated for by patient association[32] and health funds[33], in a political context in particular. This may be a key driver for the use of laboratory animals in research, but it will certainly also drive

innovation without laboratory animals, which focuses on faster, cheaper and more reliable models, and a review of the regulations surrounding the development and licensing of medicine.

- The way society thinks about ***health*** is changing: the focus is shifting from the treatment of diseases to the management of health-related conditions. People think less in terms of diseases and more about learning to live with the limitations and the finite nature of life, focusing on quality of life rather than on a cure. This may mean that certain research involving animals will become less necessary, or that less funding is available for it. The associated shift towards a healthier lifestyle and the desire to avoid certain lifestyle-related conditions may result in a reduction in the need for animal procedures for medicine and treatments, but may, at the same time, give rise to additional animal procedures, for testing foods that make health claims (lowering cholesterol, etc.), additives and food preparations, for example.
- In the Western world, we are witnessing a marked change in ***people's moral attitudes to animals and the environment.*** As a result, the use of laboratory animals in research has become a moral issue and, for some, it is morally unacceptable. This results in an increased focus on animal welfare, the replacement of animal procedures, the refinement of animal procedures and a desire for innovations and practices without laboratory animals.
- There is a debate under way within the scientific community and within society concerning the ***value of animal procedures*** for the resolution of human health and other issues, the quality of the animal procedures performed and their publication. In addition, society is increasingly demanding that information be justified (evidence-based). The growing focus on these aspects may lead to greater transparency, better (animal-based) research and less suffering. If it is deemed necessary to verify previous results with new animal procedures, it may, however, also lead to the increased use of animal procedures.
- Societal organisations, such as the Dutch Society for the Replacement of Animal Testing[34], use ***social media and crowdfunding*** to promote innovation without laboratory animals. In many cases, this pressure from society results in a political focus and pressure on innovation without laboratory animals and in additional funding being made available.
- ***Health funds*** are also increasingly realising that they play a part in the use of laboratory animals in research and that they must take social responsibility for this. From the perspective of the reliability and predictive value of research results for human patients, these funds are a key partner in efforts to encourage innovation without laboratory animals.
- The phenomenon of ***globalisation*** affects the economy, science and society as a whole. New economies are emerging, products and knowledge are being disseminated worldwide and, as a result, we are having to contend with different cultures (and different moral attitudes to the use of animals) and different, generally international legislation and regulations governing the development and licensing of medicine and substances. Given the discrepancies between the regulations in different parts of the world (e.g. between Europe, the US and Japan), animal procedures that, in many cases, are regarded by experts as "unnecessary" or as "duplication" are being performed in order to launch such products on the market. There is ever increasing recognition of the need to harmonise the wide range of regulations (test guidelines) that

apply internationally. This may result in a reduction in the use of laboratory animals in research at global level. The importance of data sharing is supported by the open data policy of the Dutch and other governments. Making data available and sharing it with others may reduce and refine the use of laboratory animals in research and may lead to a level playing field for the Member States.

These trends cannot be directly influenced, or at least only to a very limited extent, through individual policy interventions. They just happen.

Regime

At regime level, the use of animals in research is primarily influenced by factors and movements within science and legislation and regulations. These are separate regimes that are closely interlinked. Following a number of general factors and movements at regime level, these regimes are discussed individually below.

- Animal procedures have led to successes in the field of diseases and the health and safety of humans, animals and the environment, but may go hand in hand with animal suffering. In research practice, the animal model has become the "golden standard". This paradigm is perpetuated because the current scientific quality assessment system is, to a large extent, based on bibliometric criteria and because journals impose requirements on authors – e.g. the validation of data obtained through the application of an innovation without laboratory animals using animal data. In addition, in the case of a large number of animal tests, there is as yet no non-animal alternative.
- The basic principle adopted when conducting animal experiments in the Netherlands is ***"happy animals make good science".*** People recognise the importance of animal welfare for the quality and reliability of the research results obtained from animal experiments. This leads to a refinement of animal procedures.
- New (alternative) research methods must be ***validated in accordance with legislation and regulations.*** In other words, the robustness, relevance and reliability of each new method must be demonstrated. In practice, this means demonstrating that the new method or approach delivers the same or better results as the conventional animal model.
- Over the last 20 years, it has become clear that this gives rise to extremely time-consuming and expensive projects, in which multiple research institutions, both in the Netherlands and abroad, are expected to participate. But innovative approaches and research models that are based directly on mechanistic data or human patient material, for example, often provide different results that are usually more relevant to the human situation than the animal procedure. Clearly, it is difficult or even impossible to compare these with data from animal procedures. Moreover, it is generally extremely expensive to develop non-animal models and validate them in the usual way. Thus, as it stands, the validation process is hampering the development and implementation of innovations without laboratory animals, in the field of regulatory research in particular.
- Internationally, the Netherlands is a ***key player*** in the field of innovation, life science research and ICT. In addition, the principle of the 3Rs has, for a long time now, formed the basis of the legislative and regulatory structure within which research involving animal experiments is conducted.

- In the context of the framework programmes and Horizon 2020, Europe (the European Commission) has set up programmes such as the Innovative Medicine Initiative (IMI)[35], in which a large number of projects involving international consortia are carried out on innovations without laboratory animals. International, multidisciplinary projects of this nature can make a significant contribution to reduction of the use of laboratory animals in research.

The scientific regime:

- The ***scientific reward system*** is based on scientific publications in leading scientific journals and citation scores. The pressure on scientists to publish quickly, frequently and in the best journals is therefore high. These journals impose requirements, such as demonstrating the comparability of results obtained from alternative models with the conventional animal procedures. Journals that focus specifically on alternative research models (3R methods) are less highly regarded and are therefore less attractive. The emergence of open access journals and the growing opportunities for publishing unexpected and negative research results may result in a reduction and refinement of the use of laboratory animals in research.
- In the field of scientific research, scientific freedom is regarded as a "basic right": fundamental scientific research is ***curiosity-driven.*** Innovations without laboratory animals that have explicitly demonstrated that they are in the interests of research results and that have been embraced and initiated by top scientific researchers may have the potential to reduce and refine the use of laboratory animals in research. Equally, since they allow research to be carried out in a different way, innovative methods may give rise to new research questions and, as a result, increase the use of animals in absolute terms (relatively speaking, however, fewer animals may be used since more scientific questions will be investigated using animal-based research).

The legislative and regulatory regime:

- The ***principle of the 3Rs forms the starting point*** for national and European legislation and regulations with regard to the use of animals in research. In the Netherlands, this comprises a licensing system for animal procedures, of which an ethical assessment by the Central Authority for Scientific Procedures on Animals (CCD, Competent Authority) forms part. Due to political pressure, the policy on animal procedures in the Netherlands is primarily focused on a reduction in the use of animals in absolute terms.
- The partially ***decentralised*** system for assessing medicines and substances within a complex international arena makes harmonisation difficult and can result in the duplication of animal procedures. In addition, legislation and regulations (test guidelines) sometimes appear to encourage the use of animal procedures. At the very least, it is not always clear which animal procedures are strictly necessary. Obtaining acceptance for alternative methods and having them implemented in test guidelines seems to be a difficult process.
- Pharmaceutical companies and other ***multinationals*** have the power and freedom to decide for themselves whether or not they want to get involved in innovations without laboratory animals. On the one hand, to do so would be good for their image in terms of corporate social responsibility. On the other hand, some companies do not want to associate themselves in any way with the use of laboratory

animals that their products entail, or with the replacement, reduction or refinement thereof. In absolute terms, the use of laboratory animals could be reduced if this is in the multinational's interests, e.g. cheaper or faster production or licensing and PR value. Aspiring to improved patient safety through better innovations without laboratory animals could also be in a company's interests, particularly if this idea is promoted within the industry.

- Responsibility for animal procedures in the Netherlands lies with the Ministry of Economic Affairs, but animal procedures take place under the auspices of a number of different ministries (Economic Affairs, Education, Culture and Science, Health, Welfare and Sport, Defence, and Infrastructure and Environment). These ministries each have their own policy and run their own flows of grants. This ***fragmentation of policy***[36] may be counter-productive in terms of the use of laboratory animals in research. The priorities and parameters defined within the various ministries are not consistent, and coordination between departments is not considered necessary. This may result in opportunities for innovations without laboratory animals being insufficiently exploited and the perpetuation animal procedures.
- The National Science Agend[37] is an example of the increased ***involvement*** that the government offers society in determining policy on science. This has resulted in a number of routes that focus more or less explicitly on innovations without laboratory animals (Regenerative Medicine: game changer on the way to broad application; Healthcare research, prevention and treatment; Measurement and detection: everything, at all times and in any location; Personalised medicine: starting from the individual; Use of big data).

Niche

At niche level, it is primarily local factors and movements that impact on the use of laboratory animals in research:

- A number of different programmes ***promoted by the Dutch government*** are under way in the field of innovations without laboratory animals: ZonMw – More Knowledge with Fewer Animals *(Meer Kennis met Minder Dieren)*, Think Tank, Research Agenda, Top Sector Health and Life science.
- In many areas of research, innovative techniques such as imaging, telemetrics and omics are maximising the ***quantity of information per animal used.*** These techniques enable a different experimental set-up, which involves using fewer laboratory animals to achieve the same research results. Equally, innovative methods may give rise to new research questions and, as a result, may lead to additional use of laboratory animals in research.
- There is a growing focus on ***Synthesis of Evidence***[38], the experimental design and critical reviewing of existing animal models, but also on open data, data sharing and the publication of unexpected or negative research data. These initiatives by individual researchers, animal welfare bodies (IvDs) and specific research groups[39] lead to higher quality research, better animal procedures and potentially to a reduction in the use of laboratory animals in research.
- Increasingly, innovation takes place within a ***multidisciplinary collaboration***. Moreover, innovative approaches are increasingly focused on the target animal (for human medicine, humans, through the use of human cells, tissues, etc.) and on biological mechanisms. The use of innovative technologies such as organs-on-chips and the development of human-on-chips and

systems biology may lead to a reduction in the use of laboratory animals in research.
- Scientists, regulatory bodies and industry are, collaboratively if necessary, using creative methods to ***reach agreements*** on new methods or approaches and their acceptance. These interactions may accelerate the introduction and acceptance of innovations without laboratory animals.

It is clear from the above-described complex array of movements and factors that exert pressure on the use of animals in research on the various levels and in various different ways that the transition to non-animal research methods cannot be tackled in isolation by one party. It will require the involvement of a large number of players on each of the levels. It will also require multiple interventions and incentives that focus on different aspects of the issue.
The NCad therefore embraces the many initiatives that have already been taken in recent years on the various levels, which have resulted in a reduction in the use of laboratory animals in research in both absolute and relative terms and promoted innovations without laboratory animals.

Appendix 3: *Knowledge from existing reports and documents*

In the past ten years, various research groups have conducted studies from a variety of perspectives to investigate opportunities for innovation without laboratory animals, as well as the domains, technologies and strategies that offer the greatest opportunities in this regard, and the best way to encourage innovation without laboratory animals. Their findings are summarised below.

Trends in research involving animal experiments

The conclusions of the "Scientific Trend Analysis on Animal Procedures" *("Wetenschappelijke Trendanalyse Dierproeven")*, published in 2009, were summarised in the following key phrases, which, with a few additions, are still relevant today:

- *Less animals, more data*: the introduction of innovative technologies (imaging, telemetry, omics, etc.) maximises the amount of information for each animal used.
- *Happy animals make good science*: a greater focus on the health and welfare of the laboratory animal, because these affect the quality of the research results.
- *Be humane, but get the results*: the social demand for the best possible quality of life (both material and physical) without the need for detrimental animal procedures.
- *Only do what we need to know and if you do, try to understand*: a focus on the experimental design and critical evaluation of existing animal models, but also on obtaining information on underlying mechanisms in pathophysiological processes (through the use of genetically modified animals, tissue culture (stem cells, tissue engineering) and physical and chemical methods.
- *Want more, but accept less*: the increasing diversification and availability of substances, medicines and vaccines, and the trend as a society to be less inclined to accept the negative effects and side effects (risks) of these products.
- *Get more knowledge involved*: the increasingly multidisciplinary nature of research, due to the use of innovative technologies such as omics, systems biology, etc.
- *Don't modify, but change*: a radical change in testing strategy could be both an effective way of boosting the relevance of the research and an attractive route towards implementing non-animal methods.

In the "In Transition!" *("In Transitie!")* report published in late 2015 on behalf of the Ministry of Economic Affairs, the Think Tank acknowledged that "an actual reduction in the number of animal procedures requires a radical turnaround in the ways of thinking, doing and organising; the key to a transition". In the risk assessment, this completely different approach could consist of a stronger focus on exposure (and pharmacokinetics) and Thresholds of Toxicological Concern.

Technological progress means that a new development can be added to the key phrases previously formulated in the Scientific Trend Analysis:

- *Innovate, test in the target species:* the use of specific laboratory animal models and alternatives is being continuously assessed. Thanks to innovative technologies using human material or human volunteers, the transition from animal to human subjects can be bypassed in more and more cases.

The Think Tank described it as follows: "Innovations without laboratory animals include methods and developments for taking direct measurements from humans (such as smart devices and micro-dosing), technologies based on human material (such as organ-on-a-chip and organoids) or that otherwise provide useful information without the need to carry out additional animal procedures (such as computer simulations, data mining, systems biology). The strength of innovations without laboratory animals lies in the ability to further break down the existing systems of animal procedures and to give new practices the scope to develop further. Such innovations contribute towards sustainable development by taking an efficient and responsible approach towards existing knowledge from clinical and preclinical research, generating more relevant information for the benefit of patients, consumers, animals, nature and the environment, as well as optimising the development of medicine."

Societal trends in relation to research involving animals

The Societal Trend Analysis on Animal Procedures, also published in 2009, identified a number of societal tensions with regard to research involving animal experiments:

- *more different animal species:* more emphasis on substantiating animal procedures and the animal model used; the animal model should be more closely aligned to the hypothesis for the experiment;
- *more fish: g*reater focus on ecological systems and ecotoxicology;
- *more young animals:* growing awareness that organisms are more susceptible to toxicological effects during rapid growth phases, and a growing interest in epigenetics. The use of young animals may encounter social resistance;
- *growing scientific demand for primates:* growing demand for brain research as a result of population ageing and the accompanying increase in neurological disorders, and a predicted increase in the diagnosis of psychological and psychiatric conditions. The use of primates is seen as problematic;
- *safety and efficacy research:* introduction of regulations stipulating that only laboratory non-animal innovative methods may be used in safety and efficacy research for "luxury" products, such as functional foods and some nanotechnology applications;
- *lifestyle-related, old age-related, infectious diseases and food research:* increase in research in these directions, in which genetically modified animals are used in mechanistic and preclinical research. The use of laboratory animals for research into diseases resulting from avoidable, voluntarily taken high-risk actions is a subject of social criticism;
- *animal welfare research:* focus on natural species-specific behaviour, particularly of production animals, and on measures that promote animal welfare. There may be some criticism of the purpose of animal welfare research for the livestock sector; growing technologisation and the treatment of the animal as an object in business practices.

Chain responsibility

According to the Think Tank: "Our internationally renowned knowledge institutions, a wealth of innovative businesses, a growing public desire for sustainability and a culture that encourages interaction and dialogue between stakeholders provide the Netherlands with a unique position to promote itself at international level as a leader in the field of innovation without laboratory animals." However, this

will take some work. Opportunities within the domains with potential can only be utilised if all partners in the chain (science, industry, government and society) recognise the importance of innovation without laboratory animals, work together and contribute.

"The Think Tank notes… that the available scientific, economic and social potential of such innovations is not being sufficiently utilised to encourage and, where possible, accelerate the transition to high-quality research and development (R&D) without animal procedures. Among other things, this demands close international coordination of regulatory animal procedures and an emphasis on reducing the number of laboratory animals in absolute terms. Moreover, there should be a greater focus on investments throughout the knowledge and innovation chain, including funding projects to validate these innovations and bridging the period from development to dissemination and commercialisation. These latter focus areas are not exclusive to the practice of animal procedures, but are instead generally applicable to knowledge-driven innovation. Alignment with the government's innovation policy is therefore logical."

National Science Agenda

"Strategic choices and cooperation are essential to further strengthen the leading position of Dutch science. A National Science Agenda has been commissioned by the government to ensure the more targeted use of resources and energy, while focusing on scientific strengths, societal issues and economic opportunities. The National Science Agenda seeks alignment with existing research agendas such as the European research programme Horizon 2020. In the short and medium term, the National Science Agenda will have an impact on the profiles of research universities and universities of applied sciences, the planning of partners of the knowledge coalition, the direction of the development of national research institutes (Top Sectors) and investments in major research facilities. The agenda will be updated once every seven years." The Science Agenda establishes sixteen exemplary routes, of which the following may be relevant to innovation without laboratory animals:

- personalised medicine;
- regenerative medicine;
- healthcare research, prevention and treatment;
- brains, cognition and behaviour; learning, developing and thriving;
- the responsible use of big data; searching for patterns in large databases;
- sustainable production of safe and healthy food.

Priority/promising areas

The 2011 "Planning Study for Alternatives to Animal Testing – replacing, reducing and refining together" states that laboratory animal use can only be reduced by extending a generic approach to promoting the 3Rs with a targeted approach for each priority application area. The optimum research environment in which this should take place was described as *3R-aware and multidisciplinary.* The priority (promising) areas were determined based on a score denoting the scale of the problem (number of animals, animal species, suffering), the probability of success of 3R development and implementation (technical possibilities, presence of a relevant research focus and short-term objectives) and the expected impact of 3R implementation (strategic approach versus model development, specific technologies, efficiency, international profile, international

spin-off). The knowledge requirements for the priority research domains identified in the planning study are summarised as follows:

- *"fundamental research into cancer and other diseases:*
  - structuring of research into stem cells and tissue culture as part of a tiered approach;
  - targeted use and continuation of relevant omics developments and biomarkers;
- *drug development:*
  - use of current 3R insights in the development of neuropharmacology and biological products;
  - a more translational approach to the development of medicine;
- *risk assessment of chemical substances:*
  - knowledge transfer and coordination, aimed at closing the chain of development up to and including the application of innovative 3R methods;
  - research and retrospective research into combinations of 3R methods within Integrated Testing Strategies;
- *quality control of medicine, including serums and vaccines:*
  - implementation of the consistency approach when releasing vaccines;
  - collecting "reference material" through retrospective research and (concurrent) pilot projects with innovative 3R methods."

The Planning Study did not class the use of laboratory animals in education as a priority area, due to its limited scope and impact.

- *education:* the NCad views this as a promising domain. It is a relatively small domain, but one in which significant steps have been taken in recent years to reduce the use of laboratory animals. According to the NCad, the use of laboratory animals in education can be phased out entirely in the foreseeable future, at least where cats and dogs are concerned. In terms of shaping the attitudes of students, the future professionals in many biomedical research areas, the NCad feels it is particularly appropriate to opt for innovative non-animal or 3R methods over animal procedures in the education setting.

Promising areas within the legally prescribed research domain

Based on information on the status of 3R development, particularly in the regulatory domain, the NCad has sought to specify the promising areas within that domain in greater detail using information from EURL-ECVAM and the 3R implementation overview published via AltTox. In the regulatory domain, the following areas are most promising:

- *quality control;*
- *regulatory risk assessment*.

The RIVM report "Legal barriers for the use of alternatives to animal testing" states with regard to regulatory drug research that "existing pharmaceutical legislation does not impose any legal constraints on the use of alternatives to animal procedures, but neither does it actively encourage the use of these alternatives. Alternative methods are permitted, but it must be demonstrated that these have the same predictive value as animal procedures. In practice, the required validation procedure is often complicated, costly and time-consuming. There are mainly other factors that discourage the use of alternatives to animal procedures. For instance, medicines must be evaluated in accordance with strict scientific guidelines. These guidelines are not legally binding, but they do determine whether marketing authorization is eventually granted. … To encourage the development of alternative methods, regulatory authorities, researchers and

pharmaceutical companies must engage in ongoing consultation at the international level concerning the criteria applicable to such alternatives. RIVM recommends the continued promotion of research into suitable alternative methods and their implementation in guidelines."

The RIVM report "Do current EU regulations for the safety assessment of chemical substances pose legal barriers for the use of alternatives to animal testing?" states with regard to the risk assessment of chemical substances that "it is mostly practical barriers that obstruct the use of alternatives for animal procedures, and not so much legal barriers. There is, for example, a lack of alternatives for some animal procedures, or they are not sufficiently suitable or validated. It is recommended to direct attention to the removal of these practical barriers.
The study notices two other points for attention. The first concerns the use of results from alternative methods to animal procedures in the risk assessment for calamities and for the determination of industrial locations with hazardous substances. Specific results of animal procedures are often of high importance there. The results of alternative methods do not directly fit into the calculation methodologies applied by some countries for these risk assessments. Secondly, the classification, labelling and packaging (CLP) of chemical substances requires attention. The REACH framework, which is leading and for which the data used for the CLP are generated, states that alternatives are possible, on the condition that the results of alternative methods are suitable for the CLP. For some classifications, however, no alternative test methods are available, and the classification criteria limit the possibilities for developing alternative methods."

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Appendix 4: *Description of workshops in the context of the request for an opinion*

The NCad organised workshops on 9 June and 7 July 2016 in order to involve experts in the drafting of this opinion at an early stage. Experts from a number of subject areas were invited to provide the NCad with input on this opinion in a personal capacity. Twenty-eight external experts took part in the workshops. In preparation, all participants received an overview of the literature study results prior to the workshops (see Appendix 3). The aim of the workshops was to carry out an initial analysis within a short space of time (one day for each workshop) of the possibilities and impossibilities of phasing out animal procedures in the different research domains. The first workshop focused on the opportunities relating to the legally compulsory testing for the authorisation of substances and medicine. The second workshop took a broader look at the possibilities in other research areas. The NCad took the workshop results into account when drawing up its opinion, along with input from the public consultation (see Appendix 6) and input generated from the question posed via social media (LinkedIn, Twitter and the NCad website), a description of which can be found in Appendix 5.

It was confirmed during the workshops that the issue surrounding the use of laboratory animals is complex, or a "wicked problem". The word "wicked" is used here not in the sense of "evil", but rather to denote the stubborn nature of the problem and the difficulty of finding a solution. There is no linear solution to a "wicked problem".

Both workshops revealed that a large proportion of the participants were concerned about the Minister for Agriculture's request for an opinion. The request for a "phase-out timetable for animal procedures" and the desire to be a world leader in innovations without laboratory animals by 2025 show a huge ambition that the participants feel is unrealistic. Studies on molecules or on cultured cells or studies based on computer models are simpler, faster and cheaper than studies on a complete organism (animal, human being). But these are ultimately all still models: an over-simplification of how things "really" are. A living body is more than the sum of its parts. It is unavoidable that new insights are eventually verified "in real life", in an animal or human being. Some phenomena cannot be discovered at all without tests on living organisms; this is only possible within the complexity of a complete organism. Ultimately, a full understanding of the animal or human body cannot be gained through studies on isolated parts of that body (molecules, cells), or on computer models derived from them.

The participants felt that the expectation of developing viable, equivalent (and sometimes even better!) alternatives to existing animal procedures was indeed realistic in a number of specific areas. According to the participants, the main opportunities lie in regulatory research for medicines and substances. Few opportunities were identified in the workshops in relation to fundamental scientific research, although some considered the large share of this domain in the overall number of laboratory animals used as grounds for phasing out.

The workshops also revealed that the different parties do not speak the same "language". The Minister for Agriculture has requested a "phase-out timetable for animal procedures", but many participants

opposed the term "phasing out". They argue that this term suggests that phasing out is possible in all areas, a suggestion with which a large proportion of participants disagree. The experts also feel that this term does not reflect the importance of animal procedures in today's research. This could generate even greater political and public opposition to research involving animal procedures. Participants in the first workshop therefore preferred to talk about "innovation" rather than the "phasing out of animal procedures". This would create more support in the professional field. The second workshop revealed that automatically linking "innovations" to the phrase "without laboratory animals" was problematic, because innovations are not without laboratory animals by definition. It would therefore be helpful to develop a common language in the discussions on this issue, taking into account the feelings and interests of all parties involved.

The first workshop confirmed the view that the area of regulatory safety research presents real opportunities for moving towards phasing out animal procedures. This applies to both medicines and chemical substances. The participants indicated that there are a relatively large number of non-animal methods that have not yet been validated and accepted. It is worth looking into how these can be marketed. There is a difference in approach here between medicines and chemicals. One of the things the workshop examined was how to encourage the validation of existing alternatives.
The workshop also looked at other ways of achieving the purposes for which animal procedures are currently used, such as encouraging promising innovations such as stem cell technology and organs-on-a-chip. It was also established that it is important to identify "the players in the right place" and get them involved. Solid management will also be essential in order to achieve progress at national and international level. This will require a coordinated effort by many parties, including the Minister for Agriculture, who must take the lead. After the workshop, the input was elaborated using the multilayer model (MLP).

In workshop 2, the emphasis was on the opportunities for innovations outside of regulatory research. According to the participants, a transitional situation applies. It is important that the different perspectives on animal procedures and alternatives are explored: from the perspective of the professional field (why we do the things we do and why we do them in this way), from the perspective of policy (the need for change) and from the perspective of society (safety and health versus the desire for fewer animal procedures).

The debate should not focus on the laboratory animal, but on the objective of the research: to protect human health. To endeavour is the best possible science. That does not by definition mean research without animal procedures, however it could mean this if it leads to results that are more relevant (safety and health of humans, animals and the environment). In fundamental research, it is essential to perform research "without being able to predict the outcomes in advance". An animal model cannot simply be translated to the human situation, but in many cases provides more information than research at cell level. For research in specific domains, tests on an entire and living organism provide more useful answers in the context of the research topic.

During both workshops, it emerged that participants find it difficult to describe under which network and chain their own subject area falls. However, it was acknowledged that it is necessary to bring people together and to then specify what needs to be done by whom. The participants have a sound insight into what is happening in their own domains, but little insight into what is happening in other domains. They have a tendency not to look beyond their own research discipline. One possibility is to explore how to make better use of knowledge cross-over, from preclinical to clinical research. To do this, the different parties in the chain will need to start speaking the same "language". This is certainly not yet the case. It is also vital for those in leading roles to have the full overview, so that the right parties can be brought together at the right times.

There is already a great deal happening within the niches in terms of new technologies, however the participants feel that these innovations do not always lead to fewer animal procedures. In fact, new technologies can also result in more animal procedures.

A consortium could increase purchasing strength and boost progress. It could also help to encourage innovation. Examples include CRACKIT (from NC3R), Sbr (Ministry of Economic Affairs) and Vac2Vac (a project within IMI). It is not all about purchasing, but also about learning from one another by linking research. It was noted, however, that issues of continuity may be preventing collaboration between different disciplines.

Space and time must be created for validation, valorisation and implementation of non-animal methods. This process requires sound management with scope for differences. For instance, fundamental research in the context of agriculture has different values and standards with regard to research than research in the context of the life sciences.

To accelerate innovation in non-animal research methods wherever possible, there must be a focus on multidisciplinary and interdisciplinary knowledge sharing and more "generalistic" knowledge, alongside input from "experts". Sharing information is a challenge for "experts".

Within the MLP, research management seems to take place at landscape level. This is difficult to influence, because this management is carried out by major programmes. However, organising testing grounds can help to accelerate change.

Appendix 5: *Input from social media and online consultation*

In drawing up its "Phase-out timetable" opinion, the NCad aimed to gather as much input as possible from experts and the parties involved in animal procedures and replacing, reducing and refining these procedures. It did this by organising workshops (see Appendix 4) and a public consultation (see Appendix 6). In order to look beyond the circle of known experts for inspiration for this opinion, the LinkedIn group "Towards a future of scientific progress without the use of experimental animals" was set up in August 2016 (with English as the group's working language).

NCad chair Herman Koëter launched a call for ideas for this opinion in the LinkedIn group. Although the group membership reached 243 within a short space of time, there was not a particularly large amount of input. People did identify opportunities to reduce animal procedures in some areas, but also anticipated problems, for instance with regulatory authorities and government agencies. One of the participants therefore argues for greater harmonisation between Europe and the USA. "This may sound like making the challenge bigger, but it is not.
Institutes and especially companies do not only perform animal tests because they know they have to. These tests are also done when institutes or companies think that there is a chance that the knowledge from a test may be required later on in the R&D process. Research and development are not linear processes and substances/ medicines are often used for different applications than the ones that were originally expected. If an animal test is or may eventually be necessary for a marketing approval in either the U.S. or Europe, the test will be done. Therefore, the best way to the reduce the number of animal tests is to get more alignment between relevant European and U.S. government bodies on the animal testing data necessary for marketing approvals."

The NCad posted the following four statements on the LinkedIn page at intervals over a period of time. However, there was little substantive response:

1. It is possible to move away from regulatory animal testing within the next ten years. What will it take to speed up that process?
2. Progress towards animal-free innovation cannot be accomplished in isolation. If a small country like The Netherlands wants to set a new standard (and stretch the 3R-principle), cooperation on a European and international level will be essential to reach progress in animal-free innovation within fundamental scientific or regulatory research. Which steps will be necessary and which are the actors that need to be involved?
3. It is impossible to move away from laboratory animal use within fundamental scientific research within the next ten years. What will it take to reach for progress in implementing innovation within fundamental research?
4. Laboratory animals are also used for research aimed at acquiring knowledge on nature, living conditions of animals (livestock) and animal health. In most cases the animal model is from the same species as the target species. These types of research do not require a different approach towards animal-free innovation than other research areas.

Input for this opinion was also requested via Twitter and on the website www.NCadierproevenbeleid.nl . This also produced few detailed responses. Two reactions from the field of scientific research received by email emphatically stated that there are opportunities in a number of specific areas, but certainly not in all areas. The NCad was asked to be very clear about this in its opinion. Other responses from animal welfare organisations argue that much more is possible than is currently happening, and appeal to the NCad to be ambitious in its opinion: the sooner animal procedures are phased out, the better.

Areas identified as presenting realistic prospects for the development of viable, equivalent (and sometimes even better) alternatives to existing animal procedures. Examples:

- new humane organotypic slice technology, to replace studies with laboratory animal tissue. This technology is being further optimised for usability at tissue biopsy level, for example for cancer research and for more targeted treatment of cancer patients;
- alternatives to genotoxicity testing of new chemical compounds, which – before being authorised for the market – must first be tested for their potential to cause cancer. The plan is to develop an alternative to this infamous two-year chronic carcinogenity test on rats. Alongside the technical hurdles that still need to be overcome, there is also a clear policy challenge to adapt the regulations on safety requirements and procedures so that, where these tests are proven to be effective, they are also accepted and then implemented by national and European safety authorities;
- In terms of reducing the use of laboratory animals, it is realistic to expect new technology, such as molecular imaging, to be capable of saving many laboratory animals. One example is longitudinal monitoring, which makes it possible to obtain the same amount of information from one single laboratory animal as from interim cohorts that include dozens of laboratory animals. To do this, however, it would be necessary to invest in advanced image processing equipment and to make other high-throughput technological infrastructure operational with the corresponding expertise.

According to the reactions, it is a dangerous illusion to believe that it is possible to develop equivalent alternatives to laboratory animal research for all areas of research. This includes areas that are vital to the health and welfare of humans, such as:

- fundamental research of which the outcome cannot be predicted in advance, but which leads to unexpected breakthroughs that are essential for innovation;
- research on highly complex biological systems or medical conditions. Examples are many diseases associated with ageing, such as neurodegenerative conditions (Alzheimer's, Parkinson's and other forms of dementia), some cancer research, the immune system, diabetes, cardiovascular diseases or rare genetic disorders, developmental problems and so on. In these situations, complex interactions between various tissues and organs play an essential role and/or there are long-term interactions with environmental factors.

Appendix 6: *Recommendations arising from the consultation of community groups*

On 8 September 2016, the public consultation was conducted in The Hague. During this meeting, the following organisations put forward their opinions:

- Association of Laboratory Animal Science Professionals;
- Biomedical Primate Research Centre (BPRC);
- contract research organisations
- Dutch Society for the Protection of Animals
- Collective health funds (SGF);
- HU University of Applied Sciences Utrecht;
- Institute for Risk Assessment Sciences (IRAS);
- Netherlands Federation of University Medical Centres
- NV DEC
- PETA
- Dutch Society for the Replacement of Animal Testing
- Netherlands Organisation for Applied Scientific Research (TNO);
- Three R's Alternative Initiating Network (TRAIN)
- Triskelion
- Nefarma: the association for innovative medicines in The Netherlands
- Association of Parent and Patient Organisations (VSOP).

The NCad derived recommendations from the audio recordings of the meeting, which were then presented to the groups in question for approval. The invitees also had the opportunity to provide written input.

The discussion during the public consultation was structured around a number of statements. Below is a list of the recommendations for each subject that were approved by the organisations present.

Statement 1: It is possible to move away from regulatory animal procedures within the next ten years

Netherlands Federation of University Medical Centres

The question is extremely general, too much so even: regulatory animal procedures covers a very broad area. Further developments in terms of alternative approaches (comprehensive risk assessment, replacement test methods) can be expected in the case of safety tests (toxicity tests) on substances and products in connection with marketing authorisation, whereby international harmonisation between registration authorities is particularly crucial for the usability of alternative methods that have also proven valid (multicentre validation). This is less likely in all sorts of other areas (including research and education aimed at target animals), for example the study of ecosystems and species conservation, epidemiological studies, and studies with target animals in the development of veterinary drugs (equivalent to clinical studies for new medicines for human use). It is difficult to imagine that these tests will ever not be needed.
(Included in the opinion)

Dutch Society for the Replacement of Animal Testing

Legislation appears to be the inhibiting factor; however, it is also the factor that can be changed.
(Included in the opinion)

Three R's Alternative Initiating Network (TRAIN)

It could be possible to phase out toxicological and safety research within ten years, however regulatory animal procedures will not be eliminated from preclinical research and research to obtain marketing authorisation for medicines within ten years. There are different types of regulatory research involving animals.
(Included in the opinion)

contract research organisations

The international component is very important. Major initiatives such as Tox21 are very slow processes, so it will not be possible to phase out regulatory animal procedures entirely within ten years.
(Included in the opinion)

Institute for Risk Assessment Sciences

A lot can be achieved in ten years in the field of toxicology. It may not be possible to replace all testing within that time, but a lot is feasible, provided there is investment.
(Included in the opinion)

Triskelion

Ten years is highly optimistic, particularly at an international level. There is a strong focus on safety nowadays. A shift in this mentality will also be required in order to phase out animal procedures.
(Included in the opinion)

Nefarma: the association for innovative medicines in The Netherlands

The regulatory authorities have a very important voice in this debate. They largely determine what tests the industry performs. The industry is primarily looking for safe and effective drugs – animal procedures (like alternative methods) are a means of achieving this. The route to these means is to a large extent determined by international regulatory authorities. A phase-out within ten years is not a realistic option.
(Included in the opinion)

TRAIN/TNO/HU University of Applied Sciences Utrecht

Nobody has a grasp of the continuity of the investments they are making, which means that ideas are not being developed further. A transition is also required in our way of thinking: a completely different way of looking at how alternatives can be brought in. If these conditions can be met, it should be possible to phase out regulatory animal procedures within ten years. Restricting these efforts to an area that is known to offer potential is more realistic than an across-the-board approach.
(Included in the opinion)

PETA

This is one of the areas that offers the most opportunities, particularly due to toxicity testing.
(Included in the opinion)

Follow-up question: do you see opportunities to speed up the initiatives already mentioned? The steps taken towards innovation without laboratory animals, or towards phasing out. What will it take to speed up that process?

Association of Parent and Patient Organisations

This ambition of the Ministry of Economic Affairs requires a sum of two to three billion euro, which could significantly speed up this process. The funding would need to go to the collective stakeholders responsible for implementation.
(Included in the opinion)

Triskelion

The regulatory authorities need to come to a different way of thinking, to start to think differently about risk management and risk assessment. A different type of risk thinking.
(Included in the opinion)

Een Dier Een Vriend

The solution is to set a clear deadline for achieving this. Many tests are compulsory at international level, but many others are not. A great deal is possible with a positive attitude. Look at what can be done in the Netherlands.
(Included in the opinion)

Nefarma: the association for innovative medicines in The Netherlands

Focus on new technologies that will be introduced in the short term to develop new medicines, instead of dwelling on the current resources and requirements. Authorities should work with relevant stakeholders (developers, the business sector) to identify effective ways of determining the safety and effectiveness of these developments and whether this can be achieved with or without animal procedures. Adapting the current regulations is a lengthy (thirty years or more) and uncertain process, particularly considering that rules are agreed at an international level.
(Included in the opinion)

Netherlands Federation of University Medical Centres

Regulatory animal procedures take place in an international context for the authorisation of substances and products; the Netherlands cannot determine its own course. The international discourse is therefore extremely important, and transitional thinking could perhaps bring about change, although this has been encouraged for years now (e.g. different risk assessment strategies). On the other hand, it is understandable that achieving an international consensus can be a lengthy process, and authorities bear a huge responsibility for ensuring that authorised products are sufficiently safe. This is, in fact, also what the end users and politicians want.
Netherlands Federation of University Medical Centres members do not perform regulatory toxicity tests, but they do develop a wide range of research models in the context of biomedical research that could potentially be developed into innovations without laboratory animals in the context of the risk assessment referred to.
(Included in the opinion)

TRAIN/TNO/HU University of Applied Sciences Utrecht

Regulator participation in development; provide and use scope within existing legislation.
(Included in the opinion)

Dutch Society for the Replacement of Animal Testing

Social pressure is a major incentive to change the law.
(Included in the opinion)

Statement 2: It is impossible to move away from laboratory animal use within fundamental scientific research as a whole within the next ten years

Dutch Society for the Protection of Animals

This is also linked to society's ambitions. It is essential to involve citizens and put pressure on society. Keep aiming high.
(Included in the opinion)

Collaborative health funds

There are many medical research questions that require research at an organic level. This type of research cannot always be performed on humans. We feel that ten years is unrealistic.
(Included in the opinion)

Dutch Society for the Replacement of Animal Testing

It is very important that we create a mind shift within the scientific world and industry, which requires a certain amount of pressure. If that pressure is there, all of a sudden a great deal becomes possible.
(Included in the opinion)

Een Dier Een Vriend

ZonMw has major doubts about the animal model for humans. This view is not sufficiently reflected in the documents. The ambition to be a world leader in innovations without laboratory animals by 2025 is fantastic. The scope lies in laboratory animal use within fundamental scientific research as a whole: these animal procedures are not compulsory. This is determined by the government itself, and could be banned tomorrow. So ten years is entirely realistic.
(Included in the opinion)

Netherlands Federation of University Medical Centres

NFU members are all independent organisations for scientific teaching and research combined with high-quality healthcare and its continued development. The researchers, who are responsible for their research, often work together both within and outside the institution (also internationally). The UMCs bring together fundamental, translational, preclinical and clinical/epidemiological research that safeguards the medically relevant and accelerates innovation. It is rather simplistic to talk about "fundamental research as a whole". Animal procedures are carried out in a wide range of research areas (of which there are many) in the life sciences, and within this also in a wide variety of subjects and research questions. Fundamental research in the life sciences can range from field biology (such as the foraging behaviour of Great Tits) to studies on fundamental issues in biology (such as the programming and management of early embryonic development, with a strong focus on cell biology and molecular development). At the UMCs too, not every animal procedure is intended as a human model. Fundamental research is often a study of life itself, and seeks new knowledge about life.

This takes place in a context in which research methods other than animal procedures also play a large role. Fundamental research results drive science forward and are essential for breakthroughs in applied research (for example, many of the phenomena studied in embryonic research also turn out to be relevant to cancer research). If the aim is to explore alternative methods, do we have sufficient insight into what is happening and what is there? Researchers within the UMCs use various and often advanced methods to address scientific questions, the approach to which can include animal procedures where this is important.
(Included in the opinion)

TRAIN/TNO/HU University of Applied Sciences Utrecht

Why do we carry out animal procedures? When it comes to understanding diseases and specific biological processes, much more information can be obtained through innovative technologies. Yet certain research areas will still need confirmation, with an intervention to induce a disease. For ethical reasons, this cannot be carried out on human subjects, who can only be monitored if they are sick or healthy. Animal procedures will still be necessary to address these issues, although to a much lesser extent. Once we have obtained a proper understanding of these processes, animal procedures will become obsolete.
(Included in the opinion)

Nefarma: the association for innovative medicines in The Netherlands

The Netherlands is a world leader in fundamental scientific research, and this sector has therefore attracted the interest of the business sector. Many institutions have collaboration contracts with innovative companies. These collaborations will not be profitable if animal procedures are banned, because animal procedures will continue to be essential for new drug development or elements thereof. This would have an adverse effect on things like the investment climate in Dutch research and on employment opportunities, and therefore on the development of the desired knowledge economy.
(Included in the opinion)

Follow-up question: according to your members, what will it take to reach for progress in implementing innovation within fundamental research?

Three R's Alternative Initiating Network (TRAIN)

Preclinical research must be closely aligned with clinical research. Backward validation studies never happen. Investment is needed in research into why certain models do not work, so that the models are better understood and can eventually become redundant.
As long as the pharmaceutical industry is paying, it also determines which animal model is used. Reproducibility is a hot topic in the science world: all sorts of studies are not reproducible. This is one of the deciding factors. More control and less uncontrolled growth of animal models would help. Not just striving for success, but simply looking at what is going wrong in the transition.
(Included in the opinion)

Contract research organisations

The international component is just as important as the legal aspects. Sound research must be carried out to demonstrate the validity of new models. If this research is published, the new models can be pushed forward and things can be set in motion.
(Included in the opinion)

Dutch Society for the Protection of Animals

The average citizen is not aware of the "narrative" of the sector. To get this off the ground, a moral or ethical framework is needed, so that pressure can be exerted from all sides. It is difficult to reach the more informed citizens, but they do exist. Pressure must be placed on citizens, and they must be given a significant role.
(Included in the opinion)

Netherlands Federation of University Medical Centres

innovations without laboratory animals are used extensively in fundamental research, and a wide range of approaches are applied (lab methods, other models). Animals are then used to investigate whether the phenomena studied also occur in a complex organism, and animal material is extensively analysed in this context, for instance using omics technologies.
In applied research, too, animal procedures are often used to verify phenomena previously detected in vitro/in silico or postulated on the basis of similar or clinical research.
To evaluate translational and preclinical research, the predictive value of animal procedures for humans is sometimes retrospectively analysed, for instance via meta analyses of research published in the past on developments that have lead to clinical application.
A large number of publications need to be available in order to do this, and in the best case scenario conclusions can be drawn about the predictive value of frequently used models. It is important that "negative data" is also published, with sufficient technical details to be included in meta analyses or systematic reviews.
(Included in the opinion)

Biomedical Primate Research Centre

A lot is also taking place at the universities, more curiosity driven than directly related to medicine. The universities must also adopt the mindset that change is needed. The industry pays close attention to where its money is and does not want setbacks, but the universities still have great potential.
(Included in the opinion)

TRAIN/TNO/HU University of Applied Sciences Utrecht

Education and financial scope within existing lines of research. Promote the usefulness and necessity of animal procedures at a higher level than the independent research proposal of an individual researcher.
(Included in the opinion)

Statement/question 3: To achieve progress in innovation without laboratory animals in the areas of regulatory animal procedures and fundamental research, coordination at a European level is also essential. How can The Netherlands work together with Brussels, and what role do you envisage in this process for social organisations such as your own?

Three R's Alternative Initiating Network (TRAIN)

Alternatives in scientific research is an entirely different matter to alternatives in the regulatory field. One idea is to set up an association of professional groups, which can then exert pressure at an international level. An official, coordinating organisation could be the answer.
(Included in the opinion)

TNO/Association of Laboratory Animal Science Professionals

There are a number of parallel government policy lines: innovation, safety, health and replacement of animal procedures. These lines are not currently interlinked, which means that they can hinder rather than reinforce one another. There is also lack of coherence between different policy lines at European level.
(Included in the opinion)

TRAIN/TNO/HU University of Applied Sciences Utrecht

A much stricter approach could be taken to actively reviewing guidelines. No more guidelines should be introduced until a strict review has been carried out. But this does not stop at Brussels.
This really needs to be developed at a global level, however complex that may be.
(Included in the opinion)

Institute for Risk Assessment Sciences

These types of processes take a huge amount of time. The switch from LD-50 to other animal experiment developments took thirty years. And these types of processes need to be eliminated.
(Included in the opinion)

Een Dier Een Vriend

The Dutch Minister for Agriculture needs to take a very clear position in Brussels. A great deal is said, but little is agreed. If there is a clear target, a starting point can be established that must be built on. The scientists in the Netherlands themselves will then be creative enough to find different ways of working.
(Included in the opinion)

Netherlands Federation of University Medical Centres

It is important to involve the scientific organisations and professionals, including researchers, at a European level. “Brussels” plays an important role in harmonising regulations (regulatory animal procedures) and in determining the strategic research agenda designed to move the world and Europe forward in terms of life sciences, medical progress and public health, innovations (also in the face of global competition), care for captive animals and the protection of nature (including diversity and preserving species).
(Included in the opinion)

PETA

It is not just about what you can do here in the Netherlands; it is about what can be done within Europe. A number of topics are important in this context: reproductive and developmental toxicity, household products, military tissue training. Enforcement activities differ enormously between European Member States. Greater harmonisation is desirable.
(Included in the opinion)

Nefarma: the association for innovative medicines in The Netherlands

Companies currently use a wide range of alternative methods alongside animal procedures. New alternative methods are also constantly being developed, often specifically tailored to the development of a specific product. Information about this is shared at European level. It would be a good idea to carry out targeted research at European level into the need for animal procedures in drug development using entirely new technologies, whereby the regulatory process is not yet fully established).
(Included in the opinion)

Statement 4: There are a number of areas in which animal procedures are used to learn about nature, the living conditions of (farm) animals and animal health. In almost all cases, the laboratory animal used in this context belongs to the same species as the target animal. What is your organisation's view on this type of laboratory animal research?

Three R's Alternative Initiating Network (TRAIN)

As far as animal procedures in which a disease is induced are concerned, these should be approached in the same way as any other laboratory animal research. Apply the 3Rs and look at what can be achieved with tissue cultures or in silico. This also includes animal vaccines that need to be tested. The problem cannot be solved by eliminating target animal procedures; it is essential to test whether the drug offers protection.
(Included in the opinion)

Dutch Society for the Protection of Animals

This is a difficult issue. In this situation too, far from everything is in the animal's interest. Intervention in animal health will always remain linked to man's use of animals, including as domestic animals.
(Included in the opinion)

We do not by definition have the right to keep pets. And if a vaccine is developed for domestic animals, it will need to be tested on domestic animals. How logical is that actually? This is an ethical issue, also for the consumer.
(Included in the opinion)

Een Dier Een Vriend

Research carried out on farm animals is not at all focused on the health of farm animals, but rather on the more efficient exploitation of these animals. Research needs to be carried out differently, without abusing nature. Research can also be carried out on sick animals, so that no healthy animals need to be made sick. A major phase-out would then be possible.
(Included in the opinion)

Dutch Society for the Replacement of Animal Testing

This is a greater ethical issue concerning farmed animals: do we want this at all, and do laboratory animals need to be used for this purpose? Our answer to both of these questions is no.
(Included in the opinion)

Netherlands Federation of University Medical Centres

Improving the living conditions and health status of kept animals partly depends on studies using target animals. Changes must be introduced on the basis of evidence. Responsible management and policy in relation to wild fauna requires up-to-date knowledge of biodiversity, animal health and good nature conservation. Far from all research on animals in the wild is experimental; some is observational research. If this means that a sample needs to be collected at one point, it is immediately classed as an animal procedure. A very nuanced approach to this subject is therefore required, also in view of protecting the health of humans and animals and protecting ecosystems.
Based on the mission and the social role of the UMCs, a focus is also requested in this context on the quality (safety) of animal products and potential zoonotic agents (microorganisms that can occur in

both humans and animals and can cause several types of diseases). In the context of prevention, it is essential to monitor the status quo in kept and wild animals and to address high-risk trends (e.g. bacterial resistance to antibiotics). Research is essential here, and testing of the affected animals sometimes falls under the definition of an animal procedure.
(Included in the opinion)

Closing remarks

Contract research organisations

Care must be taken to ensure that the Netherlands does not become an exception to the international rule, which would have a negative impact on scientific research and the business sector in this country. Other countries view the Netherlands as an anomaly. What other countries find strange is that the Netherlands is so focused purely on replacement, and not on the other two Rs. From an international point of view, that is not what the current debate is about. By doing this, the Netherlands is excluding itself from the international discussion, making it increasingly difficult to achieve anything.
(Included in the opinion)

Dutch Society for the Replacement of Animal Testing

People with vision and courage must be given scope if we want to achieve a genuine transition. Stimulate a number of good initiatives and see what comes of them. Do not obstruct or restrict people with vision and courage.
(Included in the opinion)

The Think Tank's advisory report takes a very positive perspective and places a strong emphasis on innovation. That report is on the right track.
(Included in the opinion)

Association of Parent and Patient Organisations

Patient organisations are currently faced with drug development processes that take twelve to fifteen years. If 500 people are diagnosed with ALS in the Netherlands each year and 500 die each year, this twelve to fifteen-year period is clearly inadequate. So this ten-year phase-out is actually a small shift of the problem of development, when you view it against the prospect of twelve to fifteen years. If the patient organisations could, they would certainly speed up the process of clinical research and the marketing authorisation of medicine.
(Included in the opinion)

The process of authorising and approving medicine (including the laboratory animal process) should be sped up in relation to acceptable, lower costs, and with a risk profile associated with unmet medical needs. Associated research must continue to take place in the Netherlands. Experiments involving non-human primates should therefore not be restricted in the Netherlands for the time being.
(Included in the opinion)

TRAIN/TNO/HU University of Applied Sciences Utrecht

Something needs to be done about the infrastructure for the increased use of fresh and viable human material. An initiative has been launched to create a national supply chain for human tissue. This does not need to come at a high cost, but is more a case of ensuring proper organisation at national level.
Moreover, there is a lack of rewards and incentives to encourage organisations and individuals to do this, both in industry and in science. The introduction of a reward system, such as a "3R index", could provide encouragement to stakeholders.
(Included in the opinion)

Three R's Alternative Initiating Network (TRAIN)

It is important to not just talk about repressive measures; the sole focus is currently on replacement. There are more alternatives than simply replacing all animal procedures by 2025. The people who carry out animal procedures do so for good reasons and with results. A broader approach could be adopted, and refraining from simply pushing and repressing scientists and raising barriers would do no harm.
(Included in the opinion)

Biomedical Primate Research Centre

There is constant talk of phasing out animal procedures. It would be better to look at innovative alternatives. Naturally, this should ultimately lead to a phase-out, but it does not always need to be viewed from a negative point of view. Incentives would be a good idea.
(Included in the opinion)

Een Dier Een Vriend

A phase-out may not be what some want to hear, but it is where the emphasis needs to be placed. If we avoid using this term, nobody will know what to expect. It may be unpleasant for the scientists, but it is important that they know in what direction they should go.
(Included in the opinion)

NV DEC

If research quality is a key priority, effective preliminary research is essential. Are we choosing the right animal models to provide answers? Do the animal models provide answers? This is very important from an ethical point of view. This will automatically lead to fewer, but high-quality animal procedures.
(Included in the opinion)

Nefarma: the association for innovative medicines in The Netherlands

If we want to develop alternatives, alongside funding and regulations that make this possible, we also need a climate that allows the performance of animal procedures. Without animal procedures, we could not develop alternatives, because it would not be possible to carry out tests and make comparisons.
(Included in the opinion)

The current policy is very long and laborious, and, on top of this, a number of rules apply in the Netherlands that are unique in Europe. As a result, the Netherlands is losing momentum and missing opportunities: companies can and do move their activities to other countries.

That is not in the interest of the Dutch economy, nor of knowledge development in the Netherlands and our influence over other countries.
(Included in the opinion)

PETA

Financing and incentives are required. It is important to not just talk about phasing out animal procedures, but also to actually do it. It would be helpful to open up the licensing process and make it transparent, via an exchange of knowledge. This would also improve public understanding of the issue.
(Included in the opinion)

Dutch Society for the Protection of Animals

Various interests and various considerations need to be taken into account. We also need to look at which parties need to engage more with one another in dialogue, in order to adopt a more transitional approach to innovation. The groups involved in this discussion are too diverse to reach an agreement and to weigh up the interests of all concerned. How can we translate the different perspectives into a shared interest?
(Included in the opinion)

Written input

Contract research organisations

- Regulatory animal procedures can only be phased out in an international context, at EU level. No non-animal alternatives are currently available for testing repeated exposure or reproductive effects. Banning products tested on animals would severely hinder a large proportion of the economy. It is not realistic to phase out regulatory animal procedures within ten years in view of the international component.
  (Included in the opinion)
- In the case of fundamental research, it is important to properly validate and substantiate the alternatives so that they can be published. Efforts should be made to combine new technologies and to refine and reduce animal procedures.
  (Included in the opinion)
- The 3Rs are extremely important for animal procedures. Focusing solely on one element, like the Netherlands is currently only focusing on replacement, will not speed up the process at an international level. Striding too far ahead and not paying enough attention to our surroundings will be counterproductive, as we will be taken less seriously.
  (Included in the opinion)
- Laboratory animal research can only be carried out with good reason and when there are no alternatives. For the development of products for animals, investigating how nature works or how certain rearing methods affect the animals, unsurprisingly, the research is carried out on the same species. In view of the direct link with the species, this type of research on animals will always exist.
  (Included in the opinion)

Netherlands Federation of University Medical Centres

- It is important that the files are also acceptable to authorities outside Europe, in connection with marketing authorisation. Investments are already being made in “innovative methods”, but the road to acceptance of these mthods as a replacement for animal

procedures may be long, and should be a topic for the European agenda.
(Included in the opinion)

- From the perspective of work involving animal experiments, it is evident that a great deal of preliminary work is done before an animal procedure is set up, and also that more and more scientific information is being obtained for each animal used. UMCs have relatively easy access to human material for in vitro experimental research. There is no easy way to obtain an overview of the use of other methods. That would be desirable, but depends on resources and commitment. This type of cross-institutional project would need to be admissible in subsidy policy. This is also the only way to create a harmonised strategy and to gain a more thorough insight into what is happening.
  (Included in the opinion)
- Improper means should not be used to achieve the reductions being sought, such as a disproportionate administrative burden, cost increases and the infringement of intellectual property rights. This could lead to a loss of competitiveness. Moving to non-European countries can place animal welfare, accountability and research quality at risk.
  (Included in the opinion)

PETA

- A number of studies have shown that animal models do not work in certain research domains. The use of animal models in research domains in which these models are not suitable has hindered progress. Animal procedures should be immediately banned in these areas.
  (Included in the opinion)
- The benefit of using animal models has not yet been critically analysed in all scientific domains. A scientific systematic review still needs to be set up with regard to the suitability of animal models in those research areas where this has not yet been done.
  (Included in the opinion)
- There are certain types of research where the added scientific value never justifies the distress caused to the animal. Some researchers have called for the introduction of a "risk threshold" or upper limit to justify animal procedures.
  (Included in the opinion)
- Eliminating the use of animal procedures for regulatory purposes for which there are alternatives and promoting the acceptance of methods currently being developed will enable the Netherlands to attempt a paradigm shift from regulatory testing to innovative, non-animal methods, and in the process become a world leader in this area.
  (Included in the opinion)
- More funding should be redirected from laboratory animal studies to the development of innovations without laboratory animals. Greater investment in innovations without laboratory animals and ambitious Dutch initiatives will allow the development of more effective and reliable methods for toxicity testing, whilst at the same time reducing animal suffering.
  (Included in the opinion)

Association of Parent and Patient Organisations

- As far as European policy on animal procedures is concerned, the European patient organisations united under the European Patients' Forum (EPF) have already declared their support for the current laws and regulations on animal procedures. In the opinion of the VSOP, the Netherlands cannot deviate from European policy. *(Included in the opinion)*
- It is very important to patient organisations and funds in the Netherlands that the doctors who treat patients and researchers, with whom they often work closely in the pursuit of high-quality care, are able to pursue their medical research. Even if sometimes, at specific points, it is necessary, and even a legal requirement, to perform animal procedures for this purpose. This also applies to regulatory research into the safety and action of medicines and diagnostics.
(Included in the opinion)

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Notes

Notes currently included as an endnote

[1] The "Seventh Report on the statistics on the number of animals used for experimental and other scientific purposes in the Member States of the European Union", which was published by the European Commission in 2013, presents a statistical overview of the use of laboratory animals in the EU Member States in 2011. **http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52013DC0859**

[2] *Zo doende 2014* is the annual review of animal procedures and laboratory animals for 2014, published by the Netherlands Food and Consumer Product Safety Authority (NVWA)

[3] The 3R principles of the Replacement, Reduction and Refinement of animal procedures were introduced in 1959 by UK scientists Russell & Burch in their book "The principles of humane experimental technique" **http://altweb.jhsph.edu/pubs/books/humane_exp/het-toc**

[4] Experiments on Animals Act (Wod) **http://wetten.overheid.nl/BWBR0003081/2014-12-18**

[5] Section 1.1a of the Experiments on Animals Act (Wod) defines an animal procedure as any use, invasive or non-invasive, of an animal for experimental or other purposes, with known or unknown outcome, or for educational purposes, which may cause the animal a level of pain, suffering, distress or lasting harm equivalent to, or higher than, that caused by the introduction of a needle in accordance with good veterinary practice. This includes any course of action intended, or liable, to result in the birth or hatching of an animal or the creation and maintenance of a genetically modified animal line in any such condition, including the killing of animals solely for the use of their organs, tissues or bodily fluids for a purpose specified in **Section 1c**

[6] Zo doende 2014 is the annual review of animal procedures and laboratory animals for 2014, published by the Netherlands Food and Consumer Product Safety Authority (NVWA)

[7] In its 2015 opinion "Indicators, management and utilisation of data for monitoring laboratory animal use and 3R alternatives; Part 1" the NCad stated that "the development of 3R alternatives is not always a goal in itself, but a spin-off, and is therefore not always classified as a 3R alternative. This means that information on the use of laboratory animals and 3R alternatives is extensive, is spread over a wide range of different areas of scientific research and is not always immediately visible." **http://www.ncadierproevenbeleid.nl/adviezen-ncad/documenten/rapport/2015/11/1/ncad-advies-dataopslag**

[8] On page 16 of her 2016 thesis "Animal Testing, 3R Models and regulatory acceptance – Technology Transition in a Risk-averse Context", Marie-Jeanne Schiffelers says that the issue of regulatory acceptance and application of 3R alternatives has many of the features of a "wicked problem". In Appendix 1 to this opinion, the term "wicked problem" is defined in the context of transitional thinking.

[9] The discussion group set up by the NCad in LinkedIn in the context of this request for an opinion: "Towards a future of scientific progress without the use of experimental animals" can be found here: **https://www.linkedin.com/groups/12002776**

[10] In the current scientific quality assessment system, the focus is expressly on publications in highly respected scientific journals. Science in Transition is a movement from the field that is endeavouring, amongst others, to change this method of assessment. The founders of Science in Transition believe that "new checks and balances are required in the scientific system. Science must be valued for the social added value that it delivers and social stakeholders must be involved in the decisions concerning knowledge production. It is also crucial for the public to get a better understanding of how science works and what interests play a role." **http://www.scienceintransition.nl/** The university medical centre UMC Utrecht has already put this change into practice. An article in newspaper *NRC Handelsblad* describes the new method that UMC Utrecht has developed to assess research and researchers. In this new method, the creation of impact is key. **https://www.nrc.nl/nieuws/2016/10/26/weg-met-die-publicatiedwang-zegt-umc-utrecht-4989341-a1528550**

[11] Bibliometrics is a scientometric branch that involves gathering quantitative data on scientific activity. It creates rankings of the number of articles that particular scientists or universities publish in a year, for example. Bibliometrics does not comment on the quality of the scientific publications as such, only on the number of publications involved. Measurements in this context include, for example, citation analysis, journal impact factor and the Hirsch index (or h-index).

[12] In the context of regulatory risk assessment, amongst other things, internationally accepted innovative test methods are available for local toxicity (e.g. skin and eyes), pyrogenicity, acute oral, dermal and inhalation toxicity, dermal absorption and skin sensitisation and the mammalian erythrocyte micronucleus test. Intelligent testing strategies use a step-by-step approach that incorporates a number of different test methods.

[13] Regulatory safety research (i.e. toxicity and safety tests that are required by law) includes the following tests: Acute and sub-acute, LD50, LC50; Acute and sub-acute, other lethal methods; Acute and sub-acute, non-lethal; Skin irritation; Skin sensitisation; Eye irritation/corrosion; Repeated dose up to 28 days; Repeated dose 29 to 90 days; Repeated dose >90 days; Carcinogenicity; Genotoxicity; Reproductive toxicity; Developmental toxicity; Neurotoxicity; Kinetics; Pharmacodynamics;

Phototoxicity; Eco Acute toxicity; Eco Chronic toxicity; Eco Reproductive toxicity; Eco Endocrine activity; Eco Bioaccumulation; Eco Other; Safety test food and animal feed; Target animal safety; Other; Other efficacy and tolerance tests. This is the classification used when registering the use of laboratory animals in research, as described in the NVWA's "Explanatory notes for the registration of laboratory animals and animal procedures 2016" *("Toelichting bij de registratie proefdieren en dierproeven 2016")*.

[14] If suitable prediction models are used, the risk assessment process could take a more step-by-step approach. Prediction models of this type, which are already available and applicable, but which have not yet been accepted, include, for example: high-throughput prescreening, evidence-based assessment, quantitative structure activity relationship (QSAR), molecular toxicology for screening purposes, omics (including genomics, proteomics and metabolomics), computational toxicity and Adverse Outcome Pathways (AOP). Promising innovations for the step-by-step approach to risk assessment that are currently still being developed include, for example: organs on a chip, advanced stem cell technologies, tissue and organ constructs and systems biology (holistic approach deciphering the complexity of organisms). Use can also be made of (existing) big data, such as: high-throughput chemical screening data (US EPA ToxCast), chemical exposure data and prediction models, computational (molecular) toxicity data, including omics data, high-quality chemical structures and annotations data (EU ECHA), QSAR and 3D-QSAR data and read-across, physical chemical properties database (UNITAR, WHO), chemicals listed by associated categories of chemical and product use, clinical human data, human data from poison centres and available toolboxes (such as LRI's Ambit, OECD, etc.).

[15] Within the consistency approach, use is made of a set of quality control tests (based on physicochemical, immunochemical methods and in vitro (tissue culture) methods) and of various quality control management systems, such as Good Manufacturing Practice (GMP), Quality by design (QbD) and Pharmacovigilance data. In the European Pharmacopoeia, accepted alternative test methods are described, amongst others, for vaccines against the following diseases: NewCastle disease, diphtheria, tetanus, poliomyelitis, swine fever and hepatitis B. In addition, the batch safety test must be carried out on all batches of veterinary vaccines and the abnormal toxicity test must be carried out on all batches of human vaccines based on the monographs of the European Pharmacopoeia.

[16] Regulatory batch-based release research (batch-based quality control) includes safety tests (including pyrogenicity tests), efficacy tests and other quality control tests. This is the classification used when registering the use of laboratory animals in research, as described in the NVWA's "Explanatory notes for the registration of laboratory animals and animal procedures 2016" *("Toelichting bij de registratie proefdieren en dierproeven 2016")*.

[17] Fundamental scientific research includes research in the following areas: cancer, circulation and lymphoid organs, nervous system, respiratory system, gastrointestinal tract including liver, musculoskeletal disorders, immune system, urogenital system, sensory system, endocrinology and metabolism, multiple system research, ethology, animal behaviour and animal biology, other. This is the classification used when registering the use of laboratory animals in research, as described in the NVWA's "Explanatory notes for the registration of laboratory animals and animal procedures 2016" *("Toelichting bij de registratie proefdieren en dierproeven 2016")*.

[18] The expectation that researching of the entire organism will remain common practice for the time being applies not only to fundamental scientific research on complex biological mechanisms but also, for example, to research involving animals in which the laboratory animal is of the same species as the target animal, and for biological field research in the field of nature conservation. However, there is potential for innovative techniques in these areas too.

[19] In its 2015 advisory report "Genetically modified animals killed in stock" *("Genetisch gemodificeerde dieren in voorraad gedood")*, the NCad said that it expected that "the new innovative technology for creating GM animals, known as genome-editing, will make it possible to create a genetically engineered animal that is tailored to a specific experiment using fewer animals than is the case at the present time". The NCad also drew attention to the potential downside of this, i.e. that the use of laboratory animals could increase, amongst other reasons because genome-editing technology also makes it possible to create GM animals from other, "higher" species of animal than the mouse and the zebrafish. This could result in an increase in the use of laboratory animals, which would be at odds with society's desire for a further reduction in the use of animals in research. **http://www.ncadierproevenbeleid.nl/documenten/rapport/2015/11/26/advise-stock-animals**

[20] The report published in 2011 by the National Knowledge Centre on Alternatives to Animal use (NKCA): "Planning Study for Alternatives to Animal Procedures – replacing, reducing and refining together" *("Programmeringsstudie Alternatieven voor Dierproeven – Samen vervangen, verminderen en verfijnen")* defines knowledge areas in which the development and acceptance of 3R alternatives, combined with the effective promotion of implementation, are deemed to have potential.

[21] Applied and translational research includes research in the following fields: Human cancers; Infectious diseases in humans; Cardiovascular diseases in humans; Diseases of the central nervous system in humans; Respiratory diseases in humans; Gastrointestinal diseases in humans, including the liver; musculoskeletal disorders in humans; Immune diseases in humans; Urogenital/reproductive disorders in humans; Sensory disorders in humans; Metabolic disorders in humans; Other human disorders; Animal diseases and disorders; Animal welfare; Diagnostics; Plant diseases; Non-prescribed (eco)toxicology; Environmental protection; Animal conservation. This is the classification used when registering the use of laboratory

animals in research, as described in the NVWA's "Explanatory notes for the registration of laboratory animals and animal procedures 2016" *("Toelichting bij de registratie proefdieren en dierproeven 2016")*.

[22] The NCad's 2016 advisory report "Procedures involving cats and dogs", already recommended calling upon "the AOC Council to stop the use of cats and dogs as laboratory animals in all paraveterinary courses, whilst maintaining the quality of the paraveterinary courses". **http://www.ncadierproevenbeleid.nl/adviezen-ncad/documenten/rapport/2016/9/14/ncad-advies-proeven-met-honden-en-katten**

[23] Animal procedures are legally required or recommended for, amongst others, the following categories: chemicals, active ingredients of plant protection products, biocides, food additives, food contact materials, human and veterinary pharmaceutical products and genetically modified plants and animals. The number of prescribed animal procedures varies according to the category of substance, exposure and, in the case of chemicals, production volumes as well.

[24] Since the human genome was mapped in the Human Genome Project, scientific toxicological research has taken off. The vision and strategy of the Environmental Protection Agency (EPA) in the US in particular, with regard to regulatory toxicity research in the 21st century, has triggered a scientific movement (in the Netherlands also) that focuses on innovations for a new approach to the risk assessment process and risk policy.

[25] When validating 3R methods, ECVAM uses the PARERE network, which assesses whether a proposed 3R test meets the regulatory requirements, and it uses ESAC for the independent peer review **https://eurl-ecvam.jrc.ec.europa.eu/**

[26] In its advisory report "Indicators, management and utilisation of data for monitoring laboratory animal use and 3R alternatives, Part 1" *("Indicatoren, beheer en benutting van gegevens voor monitoren van proefdiergebruik en 3V-alternatieven; deel 1")*, the NCad recommends the creation of a data warehouse in which all the information on animal procedures and 3Rs that is available to the government is made accessible as open data. **http://www.ncadierproevenbeleid.nl/adviezen-ncad/documenten/rapport/2015/11/1/ncad-advies-dataopslag**

[27] The European Partnership for Alternative Approaches to Animal Testing (EPAA) is a collaboration between the European Commission, European trade associations and companies from seven industry sectors, and aims to pool knowledge and resources to accelerate the development, validation and acceptance of alternative approaches to animal use in regulatory testing. The overall aim is the replacement, reduction and refinement (3Rs) of animal use in regulatory testing. **https://ec.europa.eu/growth/sectors/chemicals/epaa_nl**

[28] The Access to Medicine Index has been published every two years since 2008 and is funded by the Bill & Melinda Gates Foundation and the British and Dutch governments. It ranks pharmaceutical companies in terms of their efforts to improve the availability and accessibility of medicines in developing countries in a transparent, independent way. **http://www.accesstomedicineindex.org/** One of the results of the Faster from Innovation to Humans *("Sneller van Innovatie naar Mens (SLiM)")* project, which was funded in collaboration with the Ministry of Economic Affairs, was a draft proposal for an international benchmark for the implementation of 3R methods. This stated, amongst other things, that "3R development and application is an important component of the policy on Corporate Social Responsibility (CSR). Here lie opportunities for both businesses and knowledge institutions." It should subsequently be investigated "whether funding is available for a feasibility study with regard to an international reference framework (along the lines of the Access to Medicine Index)". **http://www.innovativetesting.nl/slim**

[29] The "One Health" principle is defined as follows: "The One Health concept is a worldwide strategy for expanding interdisciplinary collaborations and communications in all aspects of health care for humans, animals and the environment. The synergism achieved will advance health care for the 21st century and beyond by accelerating biomedical research discoveries, enhancing public health efficacy, expeditiously expanding the scientific knowledge base, and improving medical education and clinical care. When properly implemented, it will help protect and save untold millions of lives in our present and future generations." Source: Kaplan et al. The brewing storm Monograph about One Medicine – One Health concept. **http://www.izs.it/vet_italiana/2009/45_1/9.pdf** In the Netherlands, there is a One Health Portal, a digital platform designed to facilitate the sharing of human-veterinary information and collaboration. Target groups include vets, doctors, people working in human and veterinary knowledge institutions and other professionals working in the field of zoonoses or the risks thereof. **http://www.onehealth.nl/**

[30] By way of comparison, reference can be made to the Agreement on Energy for Sustainable Growth, which was concluded in 2013 between more than 40 organisations. "Together, they are working towards making our society and economy sustainable. The signatories to the agreement have committed to a saving in energy consumption over the next few years of an average of 1.5% annually; a 100 petajoule saving in energy by 2020; an increase in the proportion of energy generated from renewable sources to 14% by 2020 and to 16% by 2023; and at least 15,000 additional full-time jobs." The progress of the agreements under the Agreement on Energy for Sustainable Growth can be followed online. **http://www.energieakkoordser.nl/**

[31] One example of how an individual patient used social media and crowdfunding to make treatments available is the "Help Boaz Op de Been" (help Boaz back on his feet) campaign: **http://opdebeen.nl/**

[32] On 15 September 2016, in a letter to the Minister for Agriculture, the Dutch Association of Parent and Patient Organisations (VSOP), on behalf of 16 patient organisations and health funds, said that it wanted to actively engage with and collaborate with the government and the relevant bodies in the promotion of innovations without laboratory animals, the reduction or harmonisation of legislation and regulations and the risk management process. It also said that it was crucial to Dutch patient organisations and health funds that "the doctors who treat patients and researchers, with whom they often collaborate intensively in an effort to ensure high-quality care, are able to pursue their medical research. Even if sometimes, at specific points, it is necessary, and even a legal requirement, to perform animal procedures for this purpose. This also applies to regulatory research into the safety and action of medicines and diagnostics." **http://www.vsop.nl/vsop/media/upload/pages/file/Nieuws/Zorgen_tav_beleidsvoornemens_ter_zake_dierproeven.pdf** During the public consultation relating to this request for opinion, the VSOP also stressed the importance of the rapid licensing of promising innovative methods of treatment (see Appendix 6).

[33] In this article, the Dutch Cancer Society, KWF Kankerbestrijding, discusses the issue of expensive medicines: **https://www.skipr.nl/blogs/id2850-patiënt-pil-en-dan-pas-prijs.html**

[34] The Dutch Society for the Replacement of Animal Testing has recently started proactively using crowdfunding in its campaigns for non-animal research methods. This allows the public to help fund specific research into non-animal research methods. **https://www.proefdiervrij.nl/crowdfunding/**

[35] The Innovative Medicines Initiative (IMI) is Europe's largest public-private partnership for acceleration of the development of better and safer medicines for patients. It sets up joint research projects and builds networks to encourage innovation in the pharmaceutical industry. IMI is an initiative of the European Union and the European Federation of Pharmaceutical Industries and Associations, EFPIA. **https://www.imi.europa.eu/**

[36] Back in 2008, the government's vision on alternatives to animal procedures (*Kabinetsvisie Alternatieven voor Dierproeven*) stated that government policy on 3R alternatives at that time was generally inadequate due to its fragmented nature and minimal effective support. It also referred to "insufficient transfer of knowledge and information between the different fields of research and research institutions". The government's intention at the time was to take greater control of the situation by making the knowledge of this field more coherent in terms of both content and organisation (by setting up an Interdepartmental Steering Group and Work Group on Alternatives to Animal Procedures). In this context, it planned to assume a steering, communicational, regulatory and monitoring role. **https://www.rijksoverheid.nl/binaries/rijksoverheid/documenten/kamerstukken/2008/06/09/kabinetsvisie-alternatieven-voor-dierproeven/vgp-2855846b.pdf**

[37] The National Science Agenda includes the research questions that science will focus on over the next few years. The Knowledge Coalition developed the National Science Agenda on the government's behalf. The Knowledge Coalition consists of the research universities (VSNU), the universities of applied sciences (VH), the university medical centres (NFU), the Royal Netherlands Academy of Arts and Sciences (KNAW), the Netherlands Organisation for Scientific Research (NWO), the Confederation of Netherlands Industry and Employers (VNO-NCW), the Dutch Federation of Small and Medium-sized enterprises (MKB-Nederland) and the applied research institutes (TNO/TO2). On the government side, it involves the Minister for Education, Culture and Science, Jet Bussemaker; the Minister of Economic Affairs, Henk Kamp; and the State Secretary for Education, Culture and Science, Sander Dekker. **http://www.wetenschapsagenda.nl/**

[38] In 2016, the NCad published its views on how Synthesis of Evidence can help when setting up research involving animals. **http://www.ncadierproevenbeleid.nl/adviezen-ncad/documenten/rapport/2016/5/17/ncad-advies-soe**

[39] For example, by the Systematic Review Centre for Laboratory animal Experimentation, SYRCLE (**http://www.syrcle.nl/**), and the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES) **http://www.dcn.ed.ac.uk/camarades/**

Notes

With thanks to the following experts

In preparing its opinions, the NCad makes grateful use of the services of experts in the Netherlands and abroad. Stakeholders and chain partners are also consulted. The experts consulted are not co-authors of this NCad opinion, and their views on certain matters may differ from those presented by the NCad in this opinion.

The following experts contributed to this advisory report: José Andringa (RVO.nl), Anne Kienhuis (RIVM), Andries van der Meer (University of Twente), Cyrille Krul (TNO/HU), Jan Hoeijmakers (ErasmusMC), Hans Clevers (Hubrecht Institute), Antoni Hendrickx (UMC Utrecht), Suzanne van den Bosch (SUSi), Eurogroup for Animals.

On 9 June and 7 July, the NCad organised two workshops on the possibilities of innovation without laboratory animals, within legally required and fundamental research respectively. The workshops greatly helped the NCad in determining the direction of its opinion. A total of 28 external experts took part in these sessions, including: Bob van de Water (LACDR), Peter van Meer (CBG), Pascalle van Loo (TNO), Patricia Faasse (Rathenau Institute), Stefan Braam (Pluriomics), Marie-Jeanne Schiffelers (Utrecht University School of Governance), Janine Ezendam (RIVM), Marja Zuidgeest (Dutch Society for the Replacement of Animal Testing), Ingrid Hartgers (Ministry of Economic Affairs), Jos Kleinjans (Maastricht University), Roos Masereeuw (Utrecht University), Elly Hol (UMC Utrecht), Rita Struhkamp (ZonMw), Anton Zonneveld (LUMC), Teun de Boer (UMC Utrecht), Jaap Joles (UMC Utrecht), Christine Mummery (LUMC), Terry Vrijenhoek, Bart Faber (BPRC), Peter Olinga (University of Groningen), Wout Feitz (Radboud University Nijmegen Medical Centre) and Jan Staman (Staman Consultancy).

The LinkedIn group set up by the NCad under the name “Towards a future of scientific progress without the use of experimental animals” had 230 members on 1 October 2016. Up to that date, the following group members had provided input on the request for an opinion: Rob Janssen, Brett Lidbury, Lawrence Segal, Jos Bessems, Vera Baumans, Jens Schwamborn, Jon Richmond, Dagmar Bury, Erwin Roggen, Margreet Jonker, Katleen Hermans, Karin Gabrielson Morton, Geoff Smith.

The following experts in the field representing the community groups in the Societal Expert Group for Animal Procedures and Alternatives contributed to this advisory report: Association of Laboratory Animal Science Professionals, Biomedical Primate Research Centre (BPRC), the contract research organisations, Dutch Society for the Protection of Animals, collective health funds (SGF), HU University of Applied Sciences Utrecht, Institute for Risk Assessment Sciences (IRAS), Netherlands Federation of University Medical Centres (NFU), NV-DEC, PETA, Dutch Society for the Replacement of Animal Testing, TNO, TRAIN, Triskelion, Nefarma: the association for innovative medicines in The Netherlands, Association of Parent and Patient Organisations (VSOP).

In the context of the request for an opinion, master’s students from VU University Amsterdam’s Management, Policy Analysis & Entrepreneurship degree programme, under the supervision of Tjard de Cock Buning and Eugen Popa, carried out a limited, qualitative exploratory poll on the views of various social groups on innovation without laboratory animals and phasing out the use of laboratory animals.

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