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

Evaluation of the NCad Policy Advice 'Transition to non-animal research'

Including a starting point for a follow-up Transition Policy Advice

An evaluation carried out by the Netherlands National Committee for the protection of animals used for scientific purposes (NCad)

For the laboratory animals of today and the innovations of tomorrow

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

The NCad and its methods

The Netherlands National Committee for the protection of animals used for scientific purposes (NCad) is an independent advisory body dedicated to the protection of the welfare of laboratory animals. The committee fulfils its role by providing solicited and unsolicited advice, encouraging innovation and knowledge development, and bringing stakeholders together. With this, the NCad achieves visible improvements focused on the replacement, reduction and refinement (3Rs) of animal procedures and animal-free innovation.

Members of NCad
From left to right: Roger Adan, Coenraad Hendriksen, Wim de Leeuw, Henk Smid (chair), Jan-Bas Prins, Reineke Hameleers, Katja ten Cate

Two temporary NCad members, Ellen Moors and Jarno Hoekman – experts in transition sciences – assisted NCad for the purpose of this evaluation.

Summary

In 2016, the NCad published the Policy Advice 'Transition to animal-free research', hereinafter referred to as Transition Policy advice 1.0, with recommendations aiming to boost this transition. It is characteristic of transitions that the path to the final goal rarely unfolds as previously anticipated. The NCad has therefore taken the initiative to evaluate the progress of the transition to animal-free research, and the impact of the Transition Policy Advice 1.0. Monitoring and evaluation are considered essential to visualize the progress and adjust the transition. The NCad has also asked experts for an interpretation of new insights from the perspective of transformative governance and animal ethics, aiming to include the developments in these areas in the impetus for the Transition Policy Advice 2.0.

Reflection

The evaluation was conducted through semi-structured interviews with stakeholders and qualitative analysis of interview reports. The following sub-questions were leading in the evaluation:

1. How was the Transition Policy Advice 1.0 received by stakeholders?
2. Why were the recommendations of Transition Policy Advice 1.0 followed up or not?
3. Are the regimes and landscape concerning animal-based research and animal-free innovations changing?

The evaluation provides an overview of the goals and ambitions set within the domains of efficacy and safety research, fundamental scientific and translational research, and education and training. The evaluation shows that seven themes have been decisive for the support and perception of the Transition Policy Advice 1.0 by stakeholders and the implementation of the recommendations. These are the transition goal and/or ambition, the international context, acceptance and implementation, management and ownership of the transition, economic and cultural aspects (values), funding, and monitoring of the transition.

The evaluation provides insight into drivers and barriers in the transition to animal-free research and how stakeholder groups view the transition. An important conclusion is that progress has been made in the transition, but drivers have not been sufficiently exploited, barriers have not been sufficiently removed and fundamental changes are needed to achieve the set goals.

Recalibrating principles

For the purpose of recalibrating the principles of the Transition Policy Advice 1.0, the NCad has mapped out new insights. The following questions have been asked:

1. What new and existing insights have been gathered from a transformative governance perspective to achieve the transition to animal-free research?
2. What are the existing and new insights from the perspective of animal ethics an how can or should they be included in the transition to animal-free research?
3. How is research using animals and the development of animal-free innovations funded?

The expert analyses based on new insights from transformative governance offers additional perspectives and new tools for the transition to animal-free research and emphasizes the importance of direct, society-wide change. The expert analyses based on insights into human-animal relations show that animals possess complex capacities such as communication and culture. These changes in animal ethics underline that animal welfare goes beyond the absence of distress and that notions such as integrity and agency must be included in the ethical assessment of animal research. The expert analyses on the ethical assessment of fundamental scientific research with animals exposes the complexity and uncertainty of this type of research, revealing that the current ethical framework is inadequate for this type of research with animals and that a review of this framework is desirable. Finally, an analysis of funding streams emphasizes the difficulty of obtaining unambiguous data on funding and presents estimates from reports prepared by research agencies. This is without prejudice to the fact that financing can be used as a tool to steer the transition.

Groundwork for the Transition Policy Advice 2.0

In both the Netherlands and internationally, the transition is progressing steadily with an increasingly prominent position for animal-free research in the scientific landscape. However, it is noted that the transition primarily focuses on the technical development and implementation of animal-free innovations, while aspects such as behavioural change, the phasing out of undesirable practices, a broader involvement of the social-society field, and (new) insights into animal ethics have not yet received sufficient attention. Therefore, the NCad pleads for the global transition to a society without animal experiments. The NCad formulates a number of findings and concepts from the evaluation and reviews the starting principles of Transition Policy Advice 1.0. Together, these set the stage for the broad debate on the future of scientific research with animals that will lead to the Transition Policy Advice 2.0 containing a transition path to a society without animal experiments.

Contents

Definitions

For some terms there are no unequivocal definitions, and various stakeholders, organisations or projects may have varying interpretations. The NCad applies the following definitions:

Validation of animal-free innovations for regulatory research
Demonstrating the reliability and relevance of the method for a specific regulatory application in regulatory research. Legal frameworks differ both in terms of the terminology and procedures. In safety assessment of chemical substances, mainly the term 'validation' is used. Formal validation significantly increases the likelihood of acceptance but is not a firm requirement for acceptance and implementation. For pharmaceutical products, besides the term 'validation' the term 'standardisation' is also used. Standardisation mainly focuses on the reproducibility and robustness of the method. Validation or standardisation is necessary for acceptance of an innovation in research and development of pharmaceutical products.

Acceptance of animal-free innovations for regulatory research (regulatory acceptance)
Formal acceptance of an animal-free innovation as an innovation as standardised testing method or part of a standardised testing method. There are differences between legal frameworks with regard to terminology and process. For instance, in chemical safety testing, an animal-free innovation may be formally accepted as a standardized test method by the Organisation for Economic Cooperation and Development (OECD). However, in chemical safety testing formal acceptance by the OECD, for instance, does not have a legal status. In other words, the use of a formally accepted test is not mandatory. In the research and development of pharmaceutical products, acceptance is also known as formal qualification. Qualification relates to acceptance of an animal-free innovation within a defined Context of Use. The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency's (EMA) decides on the adoption of a qualification opinion.

Implementation of animal-free innovations for regulatory research (regulatory use)

The actual application of an animal-free innovation by a regulator or manufacturer, for instance through the incorporation of an accepted animal-free innovation in legal information requirements such as in the REACH regulation or the International Conference on Harmonisation (ICH) guidelines on test procedures. The ICH also allows for future implementation of innovations by including qualification criteria for NAMs for a specific context of use. Implementation of animal-free innovations may differ across regulatory frameworks.

Acceptance of animal-free innovations for fundamental and translational research

The non-formal acceptance of animal-free innovations as a robust test carried out by the scientific field based on the publication of research results and peer review.

Implementation of animal-free innovations for fundamental and translational research

The broad implementation of innovations that do not use laboratory animals in fundamental scientific and translational research occurs through 1) acceptance by the scientific field as an alternative to animal testing; 2) conditions imposed by funders to use the animal-free innovation instead of animal testing; or 3) acceptance of the animal-free innovation as an alternative to animal testing by the authorities and committees involved in licence application procedures.

Reader's guide

This evaluation reflects a broad national and international stakeholder consultation on the extent to which the recommendations of the NCad in its Policy Advice 'Transition to non-animal research' (2016) have been implemented. This evaluation draws on structured interviews conducted with representatives of national and international stakeholder groups. This evaluation was carried out to determine whether an update of the 2016 Transition Policy Advice is required. Therefore, this report also covers an analysis of developments in transition sciences, human-animal relations, harms-benefit analyses (ethical tests) and funding streams. This evaluation explicitly does not concern the partner programme Transition Programme for Innovation without the use of animals (TPI).

The evaluation consists of a main report and various background documents. Before you is the main report. The main report is structured as follows: Chapter 1 provides an introduction. Chapter 2 gives a description of the methodology used for the analysis and a reflection on the stakeholder interviews. Chapter 3 presents the results of the reflection. For the purpose of initiating a follow-up to the Policy Advice on transition, background reports were purchased from the research firm The Business Research Company or prepared by experts in the field of transition science or animal ethics. Chapter 4 contains summaries of references to these background reports. Finally, NCad's findings and observations are summarised in Chapter 5.

The appendices provide additional information, specifically the recommendations made by the NCad in 2016 (Appendix A), the list of interviewees (Appendix B) and a detailed description of the research methodology (Appendix C).

1. Introduction

Reflection and outlook

For some time now, there has been a societal and political desire in the Netherlands to accelerate the transition to animal-free research. This desire has its roots in animal welfare considerations and the need for scientific results that are better translatable to humans. It is fair to say that the transition to animal-free research can be described as a 'wicked problem'. For various reasons, this is a highly complex issue. It involves many stakeholders, each of whom have a wide range of interests, and is difficult to delineate clearly. In 2016, the NCad intended to boost the transition by publishing its Policy Advice entitled 'Transition to non-animal research' that formulated concrete recommendations. This so-called Transition Policy Advice, hereinafter referred to as the 'Transition Policy Advice 1.0', followed a request from the former State Secretary for Economic Affairs, Martijn van Dam, to draw up a phasing-out schedule for research using animals. This request was in response to the conclusions of the Think Tank on Supplementary Financing for Alternatives to Animal Procedures in its report entitled 'In Transition! The Netherlands leads the way in innovations without laboratory animals' ('In Transitie! Nederland internationaal toonaangevend in proefdiervrije innovaties') (1). In his request, the former State Secretary endorsed the ambition formulated in the think-tank's recommendation that the Netherlands should be the world leader in animal-free innovations by 2025. The NCad's recommendations in the Transition Policy Advice 1.0 included clear transition objectives, a transition strategy and the necessity for management of the transition (see Appendix 1). The NCad made its recommendations based on the conviction that there are many opportunities to use the scientific, economic and social potential for animal-free innovations to stimulate and accelerate the transition. By formulating those recommendations, the NCad advocated for ambitious policies without losing sight of the diversity and complexity of the research field and the transition itself. Interim reflections are essential to ensure a successful transition. Typical of transitions – and this transition is no exception – is that the path to the ultimate objective is unpredictable and uncertain, and seldom as initially envisioned. In 2023, the NCad therefore took the initiative to start an evaluation of the progress of the transition to non-animal research and the impact of Transition Policy Advice 1.0.

The NCad used the multi-layer or multi-level perspective (MLP) for its Transition Policy Advice 1.0. The MLP perspective is an analysis framework that offers an accessible way to study a system and particularly offers insights and guidance for technological transitions (2). An essential fundamental premise underlying this approach

is that a transition requires a fundamental change of the regime, in other words the prevailing way of thinking, working and organising. The landscape, i.e. the layers of culture, politics and worldviews, includes features that are difficult to influence and change slowly. MLP also forms the basis of the analysis framework in this evaluation. Meanwhile, however, there is also a growing consensus in the social sciences that fundamental societal changes are necessary to address major societal challenges. An integral part of the initiation of the Transition Policy Advice 2.0 is therefore the theory of 'transformative governance', a perspective within the social sciences that may lead to practical guidance.

Scope

As long as research using animals is conducted, the commitment to replacement, reduction and refinement (3Rs) remains essential. Of more recent date is the addition of a fourth R, the interpretation of which varies, for example, with Acceleration ('versnelling') by the Dutch government or Responsibility by science and industry. Having said that, the transition extends beyond the 3Rs or 4Rs policy. It is a different approach in which research using animals is no longer the default reference point. An evaluation of the 3R policy itself was not part of this analysis, although 3R initiatives are discussed due to their contribution to and integration with the transition in practice.

Research questions

The objective of this evaluation is to assess the impact Transition Policy advice 1.0 has had. This does not involve listing the individual recommendations of the Transition Policy Advice 1.0, but a broad perspective on the progress of the transition.

The following sub-questions were guiding in this evaluation:

1. How was the Transition Policy Advice 1.0 received by stakeholders?
2. Why were the recommendations of Transition Policy Advice 1.0 followed up or not?
3. Are the regimes and landscape concerning animal-based research and animal-free innovations changing?

Interviews were conducted in 2023 as the starting point for the evaluation and to answer sub-questions 1, 2 and 3 (see Appendix B for the list of interviewees). The analysis results of these interviews were than place in a broader perspective by the NCad and supplemented with empirical findings, findings from scientific literature and research reports with the aim of initiating a Transition Policy Advice 2.0.

Besides a retrospective, it is important that the Transition Policy Advice 2.0 aligns with trends and developments in transition sciences and animal ethics. It is also insightful to be informed about the funding streams of research that use animal experiments and those that do not. The following additional sub-questions guided these objectives:

4. What new and existing insights have been gathered from a transformative governance perspective to achieve the transition to animal-free research?
5. What are the existing and new insights from the perspective of animal ethics and how can or should they be included in the transition to animal-free research?
6. How is research using animals and the development of animal-free innovations funded?

For sub-question 4, the NCad asked Professor Ingrid Visseren-Hamakers and Rebecca van Eijden, MSc., Radboud Universiteit Nijmegen, to provide an expert interpretation of the analysis of stakeholder interviews from the perspective of transformative governance. To address sub-question 5, the NCad asked Dr Koen Kramer (Utrecht University) and Dr Bernice Bovenkerk (Wageningen University), with the cooperation of NCad member Katja ten Cate, to compile two reports on progress in academic animal ethics and on new insights into the interests of animals used in research and what this means for the harms-benefit analysis in the ethical assessment. These reports are available as separate background documents on the website of the NCad: https://english.ncadierproevenbeleid.nl/

2. Methodology for the reflection on the Transition Policy Advice 1.0 and the transition in the Netherlands

This evaluation started with a series of interviews with national and international experts from various disciplines who are directly or indirectly involved in research using animals or in the associated scientific or societal debate. The central topic in the interviews was the Transition Policy Advice 1.0. However, for the evaluation a comprehensive approach was chosen that considered as many aspects as possible of the transition to animal-free research in the Netherlands. This approach provides the opportunity to consider associations between the Transition Policy Advice 1.0 with other developments, for instance with regard to innovations, financing, research culture, legislation and the societal perceptions of scientific research.

2.1 Interviews

For this evaluation, stakeholders were interviewed about the transition to animal-free research in the Netherlands. The NCad approached representatives from various stakeholder groups for the interviews, aiming to achieve as comprehensive a representation as possible of the various parties in the field (Appendix B). A finding is that among the interviewees there is an underrepresentation of the societal field, the societal research field and others outside the circle of direct stakeholders in research using animals. This finding has been taken into account in the evaluation. The interviews were conducted using a semi-structured approach to allow for the discussion of unanticipated subjects. Reports were compiled for all interviews and reviewed by interviewees for factual accuracy. To ensure the anonymity of the interviewees, quotes and excerpts from the interview reports were not included in this evaluation.

2.2 Qualitative analyses of the interview reports

Given the subjective nature of the topic, the responses to the study questions from stakeholders' perspectives, and the exploratory nature of this evaluation, a qualitative analysis of the interview reports was chosen. Two independent and analyses were performed on the content of the interview reports, by the NCad bureau and by Radboud University Nijmegen (Rebecca van Eijden and Professor Ingrid Visseren-Hamakers) using two different methods. For both methods, all interview reports were analysed by assigning codes to textual fragments based on their content.
The NCad office conducted the analysis **inductively**, i.e. without predetermined categories or codes guiding the analysis. By applying this approach, observations or categories were not included or excluded a priori. Radboud University conducted the analysis **deductively**, that is by applying categories and codes derived from the

transformative governance theory. The basic assumptions of transformative governance formed the framework for organising and directing this second analysis.

2.3 Evaluation of the progress of the transition

For the evaluation, results of both analyses were combined. In addition, the NCad conducted a complementary analysis of developments associated with the transition based on desk research and expert input from committee members.

A detailed description of the research method is given in Appendix C.

3. Reflection on the NCad Transition Policy Advice 1.0 and the transition in the Netherlands

3.1 General

The interviews revealed that there is unanimous support for the development of animal-free innovations. However, there are different insights regarding the possibilities for replacing animal research and, consequently, about what the ultimate goal of the transition should be—whether it should aim for a significant reduction in animal research or for a complete elimination. There are also different views on the speed at which the transition path can be taken. The ambition formulated in Transition Policy Advice 1.0 sparked a range of reactions following its publication in December 2016, varying from hope and optimism to concerns about the feasibility and potential hindrances to scientific research in the Netherlands. Some stakeholders perceived the Transition Policy Advice 1.0 as support for opting for animal-free innovations. Others felt that the Transition Policy Advice 1.0 was a starting point for an exploration or felt challenged to take a more critical look at scientific research involving animals, not only in terms of replacement but also refinement and reduction.

Interviewees perceived the Transition Policy Advice 1.0 as a detailed advice that carefully considers the nuances and complexity between the four domains in which animals are used, namely efficacy and safety research, fundamental scientific research, translational research and education. While the interviewees did not always clearly distinguish between the four domains in which animals are used, particularly when it came to fundamental and translational research, there is indeed a clear difference in dynamics, opportunities, barriers and stakeholders within each respective sub-transition. The general opinion is that the Transition Policy Advice 1.0 has been followed up and has contributed to the position of the Netherlands on this issue, although results are difficult to measure, and certain recommendations have not been fully implemented or adequately fulfilled.

The overarching analyses of the interview reports identified several themes that were deciding factors for the support and perceptions of the Transition Policy Advice 1.0 and the interpretation of its recommendations. These themes are listed below.

The transition goal and/or ambition

The interviews highlight that Transition Policy Advice 1.0 had the right nuance and depth with relevant recommendations. The year 2025 was named by the former State Secretary in his request for a Policy Advice, in which he endorsed the ambition

in the think tank's recommendation that the Netherlands should be the world leader in innovations without laboratory animals by 2025. In Transition Policy Advice 1.0, the NCad believed that, provided a so-called paradigm shift takes place, 'we can focus heavily on innovations without laboratory animals in a number of fields in the period up to 2025'. However, due to the communication surrounding the Transition Policy Advice 1.0, in which in particular the year 2025 became a central focus, and without a focused communication plan from NCad, the nuances were gradually lost. Consequently, reactions to the Transition Policy Advice 1.0 spanned the entire spectrum from not feasible and unrealistic to ambitious and valuable. The loss of nuance due to the focus on 2025 was also evident in the public debate, leading to heightened tensions that hindered constructive dialogue among stakeholders and did not encourage participation in the conversation. This situation was perceived as undesirable by all interviewees. Several interviewees expressed concerns about a future in which the dynamics of phasing out research using animals does not keep pace with scientific possibilities.

The partner programme Transition Programme for Innovation without the use of animals (TPI), led by the Ministry of Agriculture, Fisheries, Food Security and Nature (LVVN), has chosen to omit the year 2025 from the narrative and to eventually rephrase the ambition to 'enable the Netherlands to become the catalyst of the international transition towards animal-free innovation'. The concept of 'catalyst' was not, however, translated into concrete goals over time. Some interviewees note that the focus on connection by the partner programme TPI resulted in a search for consensus, weakening the ambitions.

The international context

All interviewees are of the opinion that international cooperation is essential if the transition is to have any impact. This was also an important recommendation formulated in the Transition Policy Advice 1.0, particularly regarding efficacy and safety testing. Interviewees indicate that there has been insufficient targeted effort on European and international collaboration.

From the interviews, it appears that the year 2025 became a key part of the communications concerning the Transition Policy Advice 1.0 (see previous section), which undermined the credibility of the Netherlands amongst several international stakeholders. This was partly because the impression was that the Netherlands would unilaterally ban the use of animals in research from 2025 onwards, without seeking international collaboration or support. Also, the feasibility of the ambition was questioned. Other stakeholders, such as international non-governmental organisations (NGOs), initially received the Transition Policy Advice 1.0 with enthusiasm, but subsequently criticised the Netherlands for not meeting its 2025 target.

Acceptance and implementation

Acceptance of animal-free innovations is necessary for broad implementation, but the specific interpretation of acceptance varies between domains. For regulatory research, acceptance by international regulatory institutions (regulatory acceptance) is essential for implementation of the model. While in fundamental research, new methods are accepted based on research results and peer review. The lack of data for acceptance and implementation, such as reliability, relevance, and replicability, is mentioned as a barrier for all domains, as is the pace and organisation of the procedures that need to be followed for these purposes. With regard to promoting acceptance and implementation of animal-free innovations, the TPI partner programme focuses in particular on facilitating multidisciplinary collaboration. Some respondents are of the opinion that, despite the diversity of partners and the ensuing collaborations, industry and fundamental scientists are not or hardly involved in the debate, yet this is necessary given their key role in the transition.

Management and ownership of the transition

Some interviewees are of the opinion that the landscape in the Netherlands has changed significantly since 2016. Animal-free innovations have received more attention within scientific research and the debate about the possibilities for reducing or replacing the use of animals in research is being conducted more openly and extensively. In the interviews, the striking statement was made that the challenge that the transition presents is that it has not one but several owners, and that progress depends on the collaboration between these different owners. However, according to several interviewees, this responsibility is felt by few of those concerned.

In the Transition Policy Advice 1.0, the NCad foresees an important role for the former Ministry of Agriculture, Nature and Food Quality in managing the transition. This ministry has fulfilled its coordinating role through the TPI partner programme, particularly from a connecting and facilitating perspective. However, some interviewees indicate that this coordinating role has not been sufficiently defined, especially

regarding strategic implementation. Expanding the coordinating role will give the current Ministry of Agriculture, Fisheries, Food Security and Nature the opportunity to take the initiative in setting frameworks and goals, thereby steering the ambition or pace of the transition. In this context, the presence and continuous investment in expertise, capacity, knowledge and decisiveness at the ministry are crucial.

Economic and cultural aspects (values)

Values were not explicitly mentioned in the interviews but could be inferred from what interviewees considered important, as observed in the deductive analysis. Interviewees were generally not inclined to refer to potential society-wide causes for the stagnation of the transition, despite their importance in the context of transformative governance. For instance, the value of the individual animal is rarely mentioned in the context of the transition. Several interviewees mentioned this as an obvious argument that does not warrant further discussion. The desire for research that is more relevant for humans is mentioned as the driver for the development of animal-free innovations. This tendency is also evident in national programmes and institutions. Some interviewees did, however, mention the pressure from society to reduce the use of animals in research, as is, for instance, evidenced by successive Ipsos-Mori opinion polls (3) and European Citizens' Initiatives on the use of animals in research that have surpassed the 1 million signatures threshold (4; 5). At the same time, very little was said about the shared responsibility of the market, consumers and citizens, with regard to the progress of the transition.

Funding

New and additional funding options were mentioned by interviewees as necessary because the existing ones are insufficient in terms of scale and scope. Financiers have an important role in steering agenda setting for multidisciplinary collaboration and critical assessment of the relevance of the proposed research model or combination of models for answering the relevant research questions. The Association of Collaborating Health Funds (SGF), for instance, puts humans rather than animals as the starting point in its vision, which is reflected in their programmes that promote the use or development of models that are based on human data or human material. Internationally, there are initiatives that take on the coordination of the entire chain and to which the Netherlands is making a substantive and/or financial contribution (see Text Box 1 for examples).

Text Box 1. Examples of international initiatives for multidisciplinary collaboration throughout the chain

PEPPER (https://ed-pepper.eu/)

The public-private partnership, PEPPER, brings stakeholders together to advance animal-free innovations for endocrine disruption research to the pre-validation stage. The Ministry of Infrastructure and Water Management has recently supported this initiative financially.

PARC (https://www.eu-parc.eu/)

In 2021, the European partnership PARC (Partnership for the Assessment of Risks from Chemicals) was launched, involving more than 200 partners from 27 countries. In the Netherlands, PARC is managed by the National Institute for Public Health and the Environment (RIVM), with as partners the Vrije Universiteit Amsterdam (VU), Utrecht University - Institute for Risk Assessment Sciences (UU-IRAS), the Netherlands Organisation for Applied Scientific Research (TNO), Wageningen University & Research (WUR), Wageningen Food Safety Research (WFSR), Radboud University Medical Center (Radboudumc), Leiden University, and the KWR Water Research Institute (KWR).Several scientific research projects are ongoing as part of PARC, with the overarching objective of establishing a permanent European and interdisciplinary knowledge development network for more efficient and effective safety assessment of chemicals. PARC supports the European Commission's ambition for an animal-free safety assessment of chemicals and is working on a roadmap proposal for 2025 aimed at achieving a paradigm shift in the legally required safety testing of chemicals in which where animal research is only considered as a last resort.

Monitoring the transition

Transition paths are dynamic and difficult to predict so it is not surprising that monitoring the transition is a complicated task. In practice, the progress of the transition towards animal-free research is often measured against the number of animal experiments performed. The absolute number of animal experiments conducted in the Netherlands has remained approximately the same, at 450,000 – 490,000 per year, from 2016 to 2022. The number of license holders has also not changed significantly. Assessing a reduction in research using animals at an individual institution is complicated by the fact that animal research may have been outsourced to third parties, for example to contract research organisations (CROs) or other institutes, because of their expertise, specialisation and the quality of the research. Additionally, animal research is sometimes outsourced to third parties because of differences in laws and regulations or not having to take direct ethical responsibility. All the interviewees mentioned the increasing and wide availability of animal-free techniques. Nevertheless, this has had no visible effect on the number of animal experiments reported annually in the Netherlands (up to and including 2022, and at EU level, ALURES up to and including 2020). That raises the question whether the reduction in the animal experiments a good measure is for monitoring the progress of the transition. However, some interviewees emphasised we should not abandon the goal of reducing the number of reported animal experiments, as we ultimately aim to see a reduction in that area. Furthermore, interviewees noted that a one-sided focus on numbers is ineffective, fails to provide sufficient context and generates resistance. Besides monitoring numbers, they call for adoption of a different method to monitor the progress of the transition with a focus on the development of animal-free innovations. Monitoring sub-domains of research or animal species would be much more informative as it acknowledges differences in dynamics and sheds more light on specific governance options. A lack of reduction in the number of animal experiments in certain sub-domains of research would prompt a closer analysis of the reasons, possible barriers and solutions within those sub-domains. In that respect, it is important to focus not only on 'what' but on 'how' the transition is managed. This kind of adaptive governance is also applied in other policy areas that can serve as an example, such as the climate policy which involves an annual cycle of setting goals, taking action, evaluating and adjusting goals and policies.

A few interviewees mentioned that steps have been taken to develop a national monitoring tool, but this proved not feasible in practice.

Key arguments underlying this conclusion included an unfavourable ratio between the time and financial investment required compared to the results, technical difficulties in linking the number of animal experiments to issued licences, the international scope of the research and the risk that the tool would continuously lag behind practice and consequently add little added value. While there are some initiatives that release information on progress (see Text Box 2 for examples), these do not appear to be known to all of those involved in animal research.

In sections 3.2 to 3.4. the above-mentioned themes are discussed where relevant for each domain.

Text Box 2. Examples of initiatives that share information about the progress in the transition

The innovation network, TPI.tv, coordinated by the RIVM, was launched in the Netherlands in 2020, with the aim to share knowledge on animal-free research. In addition, partners of the partner programme TPI apply the reflexive monitoring in action (RMA) method, developed at Wageningen University, to provide input for and steer TPI activities. From 2023 onwards, the progress report on the TPI partner programme will provide a qualitative analysis on four aspects of monitoring aimed at revealing the progress in the transition: 1) Where are we on the so-called X curve?[1]; 2) Is the focus primarily on creating new practices or also on restructuring or phasing out current practices?; 3) How are the indicators for measuring the transition task perceived retrospectively: the vision, the perspective, and the network's scope? and 4) Looking ahead, what is an important next step that will effectively accelerate the transition to animal-free innovation?

The EU's reference laboratory for alternatives to animal testing (EURL ECVAM) publishes an annual status report on progress in the development and implementation of animal-free innovations in the domains of toxicology and safety assessment, biomedical research and education.

[1] The X curve is a method to visualise the transition. It helps to interpret the phase in which the transition is currently situated, mapping not only the development of a new system but also the dismantling of the old system.

3.2 Efficacy and safety research

Regulatory research is conducted according to regulatory and legal frameworks for the authorisation of substances and medical products. In the Netherlands, 32.5% of the number of animal tests carried out in 2022 were conducted for the purpose of regulatory toxicological and safety testing (in Europe, it is 18.7% for the purpose of regulatory use and routine production) (6). Remarkably, interviewees mainly mentioned regulatory research despite the fact that the majority of animal experiments are done for fundamental and translational research. In the Transition Policy Advice 1.0, the NCad recommended phasing out the use of animals in regulatory safety testing before 2025 as a policy goal and promoting it internationally.

Table 1: *National and international authorities and regulatory institutions involved in regulatory research using animals*

Substances, pesticides and products
National authorities and regulatory institutions • The Netherlands Food and Consumer Product Safety Authority (NVWA) • Bureau REACH • The Dutch Board for the Authorisation of Plant Protection Products and Biocides (Ctgb) **European agencies, authorities and regulatory institutions** • The European Food Safety Authority (EFSA) • European Chemicals Agency (ECHA) • Scientific Committee on Consumer Safety (SCCS) • Scientific Committee on Health, Environmental and Emerging Risks (SCHEER)
Pharmaceutical products and medical devices
National authorities and regulatory institutions • Medicines Evaluation Board (MEB) • Central Committee on Research Involving Human Subjects (CCMO) • Medical Research Ethics Committees (METCs) • Official Medicines Control Laboratory, OMCL of the National Institute for Public Health and the Environment (RIVM) **European agencies, authorities and regulatory institutions** • European Directorate for the Quality of Medicines (EDQM) • European Medicines Agency (EMA) • Scientific Committee on Health, Environmental and Emerging Risks (SCHEER)

The transition goal or ambition

In general, interviewees are positive about having an ambition for the transition, but opinions were divided on specifying a year. Some interviewees feel that setting a goal with the year 2025, does not acknowledge that animal-free research alternatives are not available for all research questions. Even if the necessary innovative techniques are available, the process of development, validation and implementation requires significant time, a great deal of international coordination and availability of financial resources. This process generally needs to be undertaken separately for each application or, as in the case of vaccines, for each product individually.

The TPI partner programme was launched with the ambition of making 'the Netherlands as a frontrunner in animal-free innovation in 2025'. This ambition formed the framework within which the RIVM drafted the *Roadmap for animal-free innovations in regulatory safety assessment* in 2018 (7), partially addressing the recommendations from the Transition Policy Advice 1.0 regarding regulatory research. This agenda identifies many activities and outlines prerequisites deemed essential to achieve the ambition. Some of these activities have been implemented. However, the conclusions drawn by the RIVM in 2018, such as the need for a paradigm shift, initiating a societal dialogue about safety perceptions, developing animal-free innovations, and increasing capacity, are still relevant (see the sections below).

The international context

Internationally, ambitions for transitioning to animal-free research are increasingly being expressed. The European Commission has also paid more attention to this transition. This is being encouraged further by the European Parliament and the 'Save Cruelty Free Cosmetics — Commit to a Europe Without Animal Testing' European Citizens' Initiative (4). In response to this European Citizens' Initiative, one of the Commission's commitments involved the development of a roadmap to phase out the use of animals in regulatory safety testing of chemicals. The Canadian Senate passed a law in 2023 requiring the government to present a concrete plan within two years to phase out the use of animal testing in safety testing (8). The US EPA (US Environmental Protection Agency) had committed in 2019 to phasing out animal testing in safety research, with 2035 as the deadline. However, recently the EPA updated this by aiming for a significant reduction in animal testing without specifying a particular year (9).

These developments suggest a cautious acceleration internationally and momentum in the replacement of research using animals. Yet the general opinion in the interviews is that little has been done nationally in the Netherlands to implement recommendations set out in the Transition Policy Advice 1.0, that pertain to the international arena. Despite increasingly progressive voices from major European agencies, animal testing is still largely used as the default starting point to meet information requirements for market approval. There are still significant barriers, and opportunities left unexploited. Some interviewees noted, for instance, that European initiatives often rely on the 3Rs principle (replace, reduce and refine), which takes animal testing as a starting point even though the essence is about opting for the best model for the purpose of the study.

Another key issue, particularly perceived by the industry as the main barrier, is the absence of global harmonisation of laws and regulations. Because of the global – not (only) European – market, many companies benefit greatly from laws and regulations that transcend the level of individual countries. Whereas one country may accept animal-free alternatives, another may still require the results of research using animals for market approval. As a result, research using animals is requested and conducted despite the availability of animal-free innovations, which may discourage the industry from investing in these innovations. It is worth noting that few interviewees provide an analysis of the international power dynamics and how this aspect is dealt with. Additionally, 'the push and pulls' for the transition of political economic systems, such as the free market or globalisation, are not mentioned. Political economic systems are linked in two ways to the role of consumers in the transition, given that the free market is not only demand-driven; it also creates demand.

Validation, acceptance and implementation

The development of new animal-free innovations towards validation, acceptance and subsequent implementation is a tailored, time-intensive and costly trajectory.

A few of the interviewees noted that by accelerating efforts on validation, acceptance and implementation, the EU could generate more confidence in animal-free innovations. In this respect, it remains essential to stay engaged internationally and keep the subject on the agenda. International acceptance of animal-free innovations is taken into account, for instance, in the development of the European roadmap to

phase out animal testing for chemicals (10). EURL-ECVAM coordinates the validation of animal-free innovations for chemicals and pesticides in Europe. NETVAL is the network of laboratories in Europe responsible for performing the validation at EURL-EVCAM's request. Several Dutch institutes and companies are affiliated with the EU-NETVAL network of reference laboratories. During the process of efficacy and safety testing for pharmaceutical products, the terms standardisation and qualification are used, which is necessary for implementation. In Europe, the Scientific Advice Working Party of the EMA (EMA-SAWP, a standing working party providing scientific advice) is responsible for guiding the qualification process for animal-free innovations. In consultation with experts, the EMA-SAWP gives recommendations regarding possible formal qualification by the European Committee for Medicinal Products for Human Use (EMA-CHMP).

Many animal-free innovations never reach validation/standardisation and implementation but fail to progress during or beyond the development stage. This is also referred to as the 'valley of death'. The barriers identified and elaborated below include:

- the lack of funding;
- insufficient anticipation of validation and implementation;
- and/or the failure to adapt regulations and information requirements – or the length of time taken to do so.

Funders appear reluctant to support further development financially, perceiving this research as less innovative and at the same time still too fundamental and far from actual regulatory application. In the interviews, the picture emerged that, for these and other reasons, further development of innovations is unappealing and unfamiliar to academic researchers. Also, for industry, the path of further development is risky due to the uncertainty related to quality, replicability and regulatory application potential of animal-free innovations However, there is a gradual change among Public funders. A prime example of this was the Dutch Research Agenda's call on acceptance of existing animal-free models, which was honoured in 2023 (11). Another example is the third subsidy round of the Human Measurement Models programme initiated by the Association of Health Funds (SGF), Health Holland and ZonMw, which started in 2024 and made available €5,4 million. This new round is committed to the further development of models to avoid the 'valley of death'.

In addition, models often fail if insufficient attention is paid during the development phase to the possible follow-up trajectory to application. Acceptance and implementation are therefore increasingly becoming focus points in multidisciplinary collaborative projects by involving not only developers of the model but also end-users, such as the industry and regulators, as soon as possible without compromising the independence of the model assessment.

The interviews highlight various arguments for industrial partners to contribute to the transition and invest in the development or further development of animal-free methods. Social responsibility and improving animal welfare are cited as logical arguments, reinforced by ongoing societal pressure. In some interviews, it was noted that for the industry, the desire for the most translatable model, rather than the replacement of animal research is the priority. Once the development, validation and implementation process is completed, there are often also benefits for industry, for instance because animal-free innovations can be cheaper to implement, such as in the quality control of veterinary products. There are examples where these models are more robust compared to research using animal.

Interviewees pointed out that industry's implementation of animal-free innovations is only the obvious next step if they are accepted by regulators. In previous research, the RIVM concluded that there are effectively no legal barriers to the use of animal-free innovations. However, the application of animal-free innovations is not encouraged sufficiently even within Europe, leading to hesitancy in using them in the market approval process because of the risk that research using animals may still be required due to other European laws and regulations, causing delays. A notable example is the animal-free innovations for eye irritation and skin sensitisation, that have been fully implemented under European cosmetics legislation. Nevertheless, animal testing for these purposes is not banned within all other European legal and regulatory frameworks. Instead, it is allowed under certain exceptions. In practice this can lead to having to carry out the animal experiments. In addition, in practice, acceptance of an animal-free innovation in Europe does not automatically mean that the innovation will also be recognised by authorities beyond the EU borders. This is where international harmonisation of regulations offers opportunities, but harmonisation is a difficult process. Consequently, a company may be able to use an animal-free method for product registration in Europe but not for registration

outside Europe. In that case, the company will still need to conduct the traditional test using animals for registration outside Europe.

Specific legal information requirements may also be a barrier if the requested information is specific to research using animals. In practice, complete replacement of animal experiments is proving challenging in these cases. A crucial observation in this and other evaluations is that phasing out animal testing in efficacy and safety testing is ultimately impossible unless there is a paradigm shift where the focus moves from animal-free alternatives to the information necessary for efficacy and safety assessments. In this context, the RIVM mentions a revolutionary approach aimed at animal-free regulatory research, where the focus is not on information *requirements* but information *needs* (12).
For this, it is necessary to build confidence in an alternative approach to validating and qualifying animal-free methods for assessing efficacy and safety that is rooted in human biology and physiology, unless it concerns products intended for application on animals. This necessary paradigm shift has been increasingly acknowledged in recent years and is being explored step by step. In the Netherlands, the five-year project Virtual Human Platform for safety assessment (VHP4Safety), funded by the Dutch Research Agenda Program: Research along routes by Consortia (NWA-ORC), was launched in 2021. This project focuses entirely on a paradigm shift. The project is coordinated by the Utrecht University together with the RIVM and the HU University of Applied Sciences Utrecht. The VHP4Safety consortium integrates several scientific disciplines and facilitates collaboration with stakeholders, including societal stakeholders, aiming to establishing a data platform based on human biology and physiology that can be applied in an animal-free safety assessment.

Management and ownership of the transition

Various stakeholders are involved in the chain and the various stages of development, validation, acceptance, and implementation of animal-free innovations in regulatory research. Awareness of the 'valley of death' is rising and steps are gradually being taken to mitigate this phenomenon, but it remains a significant barrier in the transition. Overcoming these barriers and capitalising opportunities requires those managing the process to set a clear course towards interdisciplinary research and implementing strategic national and international policies. Following this, it becomes crucial to continuously facilitate and promote the movement towards interdisciplinary research. The government is uniquely positioned as the stakeholder to take on this leadership role and delegate responsibilities to other stakeholders effectively.

At a policy level, there is increasing attention to promoting the Dutch ambition internationally. So far however, input from the Netherlands on acceptance and implementation of animal-free innovations within regulatory research and as part of the revision of regulatory information requirements, is only being coordinated to a limited extent. For instance, there is no known European or international strategy to systematically promote animal-free innovations. The interviews reveal that as a result, there is too little insight into the position taken on the international stage and the reasons why some recommendations have not been followed up. An example is the 'safe harbour' concept, of which some interviewees know that some action was taken of but do not know why it failed (see Text Box 3). The revision of the REACH regulation (i.e. the European regulation on the manufacture and import of chemicals), originally planned for 2023, is another example of an opportunity to boost the replacement research using animals by giving laboratory animals a less central position in the legal information requirements. For this, it is crucial to have coordinated national input in the pipeline that is aligned with other Member States. This contribution must, however, represent all the necessary areas of expertise in the field of animal-free innovations, for which coordination between the ministries is also necessary.

Text Box 3. Safe harbour

In the Transition Policy Advice 1.0, the NCad recommended advocating internationally for the establishment of a safe harbour — after the example of the FDA's safe harbour — where opportunities for innovative ideas can be developed and compared without the interference of laws and regulations. The concept of a safe harbour has been explored by various stakeholders over the past few years and it was also a recommendation in the RIVM's 'Roadmap for animal-free innovations in regulatory safety assessment' and the 'Knowledge Agenda on the Transition to Non-Animal Innovations' by ZonMw (7; 13).

In Europe, the EMA attempted to implement the safe harbour concept through the EMA Innovation Task Force. This initiative encourages industry to submit data from innovative methods, allowing for a free exploration of the strengths and weaknesses of these methods in a confidential manner, thereby enabling regulators to become familiar with new models at an early stage. The assurance is given that the information from these innovative research methods will not be included in the regulatory decision-making process. However, this proposal has not yet been utilised (14). The SCCS (Scientific Committee on Consumer Safety)[2] also applied a similar interpretation of the safe harbour principle in the risk assessment of a UV filter for which an 'ab initio' dossier was submitted with a next generation risk assessment (NGRA) approach, in addition to a standard safety dossier. The SCCS used this ab initio dossier to study the pros and cons of this innovative approach.

Financial and cultural aspects (values)

From the interviews, it is evident that that values regarding safety weigh the heaviest and that regulatory research is extremely risk averse in terms of how it is structured. This risk aversion exists to varying degrees among all stakeholders in the chain. There is considerable trust in data generated from research with animals, partly due to the stringent quality standards mandated by legislators for these tests.

[2] The SCCS is an independent scientific committee appointed by the European Commission to assess the safety of consumer products, such as cosmetics and toys, and ingredients, such as dyes and preservatives.

However, there appears to be little attention given to uncertainties intrinsic to the animal test being used. A widely held perception is that research using animals has limitations and often does not translate well to humans. Nevertheless, the impression from interviewees is that the risk of safety incidents is more likely to be accepted if existing guidelines have been followed, rather than if a reasoned decision to use an animal-free innovation has been made. As a result, there is reluctance to completely replace research using animals with animal-free innovations.

Some interviewees have the impression that this sentiment is reflected in society: safety and risk minimisation have become increasingly important themes for the general public as shown, for instance, in the 2024 EU barometer 'Attitudes of Europeans towards the Environment' (15), even though there will always be margins of uncertainty. However, citizens are not actively involved in the debate about the actual risks and perceived risks. The conversation about risk acceptance and society's perception of safety, as well as the position that animal-free innovations and animal testing take in this context, is currently insufficiently addressed. Moreover, the paradigm shift necessary for animal-free regulatory research requires not a different interpretation of the information obtained from historical research with animals, but a completely different approach to safety and efficacy that takes humans as its starting point, thereby necessitating a different approach to research and assessment.

Monitoring the transition

In 2016, the NCad advised prioritising the monitoring and evaluation of the number of animal experiments and the availability of knowledge about innovations and 3R alternatives. International institutions regularly report on new and existing alternatives, and the specific animal experiments that have been replaced. For instance, the European Chemicals Agency (ECHA) publishes a report every three years, in accordance with the REACH regulation, about the use of alternatives for the purpose of chemical safety research and activities to promote their use (16). Similarly, the EURL ECVAM publishes an annual status report of its activities in the development and implementation of animal-free innovations and activities to promote the acceptance of innovations in regulatory research (17). However, there is currently no transition monitoring tool available that provides a broader reflection beyond just the development and implementation of animal-free innovations, including other

aspects such as the objectives, role, position and responsibility of stakeholders and the existing system.

3.3 Fundamental scientific and translational research

In 2022, fundamental scientific and translational research accounted for the majority of total animal use, about 48.9% of the total number of animal experiments reported in the Netherlands (18) (about 72.0% in the EU in 2022 (6)). The Transition Policy Advice 1.0 recommended formulating target images with transition goals for each sub-domain of fundamental research. For translational research, the NCad recommended the Netherlands to take an international leadership role in development of animal-free innovations. In the interviews, a clear distinction between fundamental and translational research was not always made, partly because fundamental research often gradually transitions into translational research.

The transition goal or ambition

Fundamental scientific research and translational research are the driving force behind animal-free innovations and is therefore indispensable to the transition. However, an animal-free innovation is not always recognised as such but rather seen as simply a new method in the context of scientific progress. Animal-free innovations are mainly seen as complementary to research using laboratory animals.
The group of researchers that, for various reasons, commits to animal-free research is gradually growing and is aware of the necessity for multidisciplinary collaboration between specialisations.

On the other hand, fundamental research has a strong tradition and long history of using animals in research, which must not constitute a hindrance for the transition. Illustrative reasons for the research tradition include:

- the various animal-free methods do not sufficiently represent the complexity of the target organism and are not yet sufficiently developed to be able to replace all animal tests. At the same time, the lack of an effective translation of the use of animals is endorsed;
- research aimed at animals should really be conducted in the species concerned; and there is a notion that things can be done with animals that are not allowed to be done with humans;
- there is a lot of experience with animal testing, a lot of historical data to build on and the applicability domain is known while it is also acknowledged that the reliability of animal testing data is problematic (19).

Additionally, in interviews and literature (for instance in a recent study on the preference for animal research in the peer review process (20)) it is noted that animal research is often required for the publication of research in high-impact journals, which in turn contributes to funding opportunities for research. Indeed, funding for fundamental science research is primarily based on scientific quality, measured by the numbers of publications, the impact factors of the journals and the number of citations. The implementation of a different quality assessment system, such as DORA (21), which explicitly includes societal research relevance and impact, is seen as the future for evaluating science, and this will prompt a change in the research tradition. The changing view on the valuation of research, for instance through the national Recognition & Rewards programme[3] and the Recognition & Rewards initiative,[4] is also contributing to changing the research culture because aspects such as societal relevance and the impact of research results are taken into account. These factors were occasionally mentioned in the interviews and opportunities and barriers ensuing from this were not discussed.

Some interviewees referred to the target images as a visible and valuable implementation of the Transition Policy Advice 1.0 by fundamental scientists, in which goals for specific research domains are explored and identified. However, they also indicated that the follow-up process after publication of a target image is unclear, which compromises the potential impact of the target image. For instance, no responsibility has been assigned for a coordinated implementation and follow-up of a target image, nor for the necessary funding. In addition, there appears to be tension between setting ambitious goals in the context of the transition to animal-free research and creating sufficient support for a target image. Partly because of this, not all the target images drawn up so far meet the principles defined by the NCad. Dialogue with patient and animal advocacy groups and transition experts is one of the principles for creating these target images, but this did not happen: the target images were created

[3] https://www.nwo.nl/erkennen-en-waarderen

[4] https://recognitionrewards.nl/

by the scientific community without input from the societal field. In this context, it is advisable to involve stakeholders from the social and societal expertise area in the future as the desires of the societal field may not align with what the scientific community wants or perceives that the society wants.

The shift in focus towards reducing research using animals and encouraging the development of animal-free innovations is more evident in the industry, which is increasingly making its voice heard in public. In this sector, obstacles such as the pressure to publish and dependence on funding, are not an issue. In this context, industry is increasingly seeking collaboration with academic institutions. Prime examples of this are Create2Solve, an initiative of the Netherlands Organisation for Health Research and Development (ZonMw) which supports the development of impactful animal-free innovations, and the public-private consortium VAC2VAC[5] that is committed to develop animal-free test methods for vaccine quality control. That said, industry as a private partner, has other responsibilities and interests to take into account, such as societal responsibility, laws and regulations, and competitive interest.

The international context

By definition, fundamental science has an international character, manifested through various means such as international collaborations, international platforms, attracting international talent and publishing in international journals. There is limited insight into the developments in and the influence of the international context of fundamental research on the transition to animal-free research. In the interviews, there was little reflection on this aspect, although several interviewees noted that cultural differences in the value placed on animal research and animal welfare are affecting the progress of the transition to some extent.

Although animal-free innovations are the subject of research in several international projects, as noted earlier, they are by definition not always recognised and acknowledged as contributing to animal-free research. A specific example mentioned in the interviews is the projects carried out within the European IMI (Innovative Medicine Initiative) public-private partnership. This initiative aims at overcoming bottlenecks in the development of medicinal products. Although these projects were not presented as 3R projects, a significant portion of them yielded 3R results, including animal-free innovations. Recently, in its response to the European Citizens' Initiative 'Save Cruelty Free Cosmetics — Commit to a Europe Without Animal Testing', the European Commission decided to submit a proposal within the European Research Area (ERA). The purpose of the ERA policy instrument is to coordinate EU Member States' innovation policies and focus on collaboration. One of the aims of the ERA policy action is to prioritise the development of animal-free methods in biomedical research. The Netherlands is a frontrunner in this initiative.
EURL-ECVAM has also published several reviews on the use of animal-free innovations in biomedical research (22) and is working on developing an AI-driven environment for finding animal-free methods. To strengthen the connection with international developments, ZonMw has recently also made funding available at the national level to enhance the findability of animal-free research methods using AI[6].

Acceptance and implementation

The interviews reveal that initiatives for developing animal-free innovations primarily emerge to fundamental research questions where research using animals does not bring solutions closer, usually due to low translatability. For these research questions, innovations are more readily accepted by colleagues, and in these situations, it proves feasible in practice to overcome significant obstacles such as securing funding, building expertise and developing new techniques. It is likely that there are more research questions where animal-free innovations could offer opportunities that are currently not recognised due to the tendency in science to publish negative results only to a limited extent (see, for instance, a recent study on the publication of research with animals conducted at two German university medical centres, which found that 33% of the research was not published (23)). Additionally, some interviewees observe a general movement in science towards a more critical attitude to research using animals. Even if animal testing is considered necessary because no options for replacing it are to hand, there is increasing attention for reduction and refinement from an animal welfare perspective, for example with regard to housing and care.

[5] Innovative Health Initiative VAC2VAC. Vaccine lot to vaccine lot comparison by consistency testing: www.ihi.europa.eu/projects-results/project-factsheets/vac2vac

[6] ZonMw funding possibility: Unlocking Animal-free innovations from the literature. [Ontsluiten Proefdiervrije innovaties uit de literatuur] [only in Dutch]. https://www.zonmw.nl/nl/subsidie/ontsluiten-proefdiervrije-innovaties-uit-de-literatuur#orientate-wherefor

Nevertheless, there is still much to be gained in terms of acceptance and implementation of animal-free innovations. Specific opportunities mentioned in the interviews include increased and targeted funding, multidisciplinary research to familiarise researchers who use animals with animal-free methods and to bring them together with experts in that field, and fostering a new culture where innovations are carried out in parallel with and independently from research using animals. Investments in parallel studies and in the validation of animal-free innovations contribute to the desired transition. The changing perspective on the appreciation of research, for instance through the three previously mentioned DORA initiatives, the national recognition and reward programme and the Recognition & Rewards initiative, also contribute to a change in the research culture and encourage acceptance and the implementation of animal-free innovations.

It was mentioned in the interviews that in translational research, where there is a direct relationship with human data or human material, insurmountable limitations in translation are prompting more researchers to focus, whether completely or partially, on animal-free innovations. In the research into innovative medicines, for which there are no regulatory guidelines yet, there is for instance an increasing search for animal-free innovations that better align with the target organism. An example mentioned in the interviews, where the Netherlands is actively advocating for animal-free regulatory guidelines, is advanced therapy medicinal products (ATMPs)[7] (24). This gradual shift towards animal-free research is being driven by the increasing availability and possibilities presented by model systems using human cells and human stem cells, such as organoids and microfluidics, and other approaches, for instance using imaging techniques, artificial intelligence and molecular or biochemical techniques. Large-scale implementation of these models, however, lag behind and is being impeded by the lack of validation and acceptance. What would help, according to some interviewees, is greater awareness and attention for standardisation and agreements about the quality requirements that innovations must meet. Efforts are also being made in the fields of fundamental and translational research to improve the translational value of research using animals, including genetic modification. This mitigates or removes the limited translational value of some models as drivers of the transition.

Several respondents mentioned that research involving human subjects or human material is an important pillar in the transition. Compared to animal-free innovations, research results obtained from human subjects or human material are confronted with fewer barriers in terms of acceptance and implementation.
The main barriers come from the ethical and methodological restrictions of research involving human subjects. However, there is an increasing focus on developing and improving techniques to enhance human subject research, for instance using more advanced imaging techniques. The urgency to promote human (relevant) research is also shared by funders, such as ZonMw or the previously mentioned Association of Health Funds (SGF) that actively encourages the use or development of models based on human data or human material.

Management and ownership of the transition

Although not explicitly stated, interviewees did allude to the responsibility for the transition in fundamental and translational research. Collaboration, where various researchers put forward their expertise, has always been a cornerstone in fundamental and translational research and is typically done in within their own fields and perspectives. However, a paradigm shift calls for interdisciplinary collaboration. In the interviews, directors and funders are mentioned as the two parties who share responsibility for the transition. A key initiative in this is the Knowledge Agenda for the Transition to Animal-Free Innovations that ZonMw drew up in 2023. Based on close consultation with those in the research field, it describes various obstacles and solutions for the transition and makes recommendations to various stakeholders, including research funders, ministries, knowledge institutions and training institutes (13). Furthermore, the experience shows that a transition within an institute is very challenging unless embraced and facilitated by its management board. Utrecht University is cited as an example where several research lines and supporting facilities have been set up for the purpose of animal-free research and for which additional funding has been made available.

Financial and cultural aspects (values)

One of the most important values in fundamental research in particular is that of scientific freedom. Scientific freedom is about shaping research based on

[7] ATMPs are medicinal products that have compounds based on genetic material, cells or tissues and are used for somatic cell therapy, gene therapy and tissue engineering. An example of a combined ATMP are cells embedded in a scaffold.

engagement and social values, as argued in the Royal Netherlands Academy of Arts and Sciences' Academy Lecture 2023. Scientific freedom presuppose critical thinking and the courage to doubt and requires the scientist not to impose his or her own scientific or moral truth on others but instead is always willing to participate in the debate. The same applies to the debate on the transition and research using animals. The interviews show that scientific freedom is seen as a given, but it is unclear whether everyone views scientific freedom in the same way as presented in the 2023 Academy Lecture. Scientific freedom cannot be considered an absolute right under all circumstances. When it concerns research using animals, the interests of scientific freedom must be weighed against the interests of the animal within the applicable legal frameworks. In Sections 4.2 and 4.3, we elaborate on the need to reconsider the position and interests of the animal as well as the application of the harms and benefits analysis. These considerations are highly relevant to the transition in fundamental research.

The NCad, in collaboration with the RIVM, commissioned an exploratory study by the research and consultancy firm, Inspire to Act, entitled: 'Exploratory study on the rationale and drivers influencing methodological choices'. This report is available as a background document to this evaluation (25). This exploratory study examines the rationale and drivers influencing methodological choices in fundamental cardiovascular research. This particularly concerns gaining insight into the decision-making regarding the choice for a model for answering a scientific question in the light of scientific freedom. It concerns a small-scale study in which a literature scan and in-depth interviews were carried out. The study revealed that there are different occasions when a choice can be made to conduct scientific research with or without animals. In addition, the characteristics of inter- and intrapersonal aspects, tasks, the organisation and the institution all play a role in the final decision. The study also examines which barriers might prevent the possible use of animal-free methods and which parties have a strong influence on the choice and use of research with animals or animal-free methods.

The main takeaway points that emerged from this study for a more conscious choice of which particular research method to use include:

- enhancing knowledge by:
  - paying more attention to research models and method-based working during the study programme;
  - systematic reviews;
  - scientific publication of research which has been conducted properly from a scientific perspective but that does not demonstrate any effects;
- increase competency for multidisciplinary working practices;
- make funding available for the innovation;
- encourage working in consortia and in multidisciplinary teams;
- stimulate validation research.

The study also suggests that the following people and parties have a lot of influence on the choice and use of animal testing:

- professors and/or principal investigators;
- collaboration partners (multidisciplinary teams/external work contacts);
- research funders;
- the pharmaceutical industry;
- politics, the media and the societal debate;
- editors and reviewers at high-impact journals;
- laws and regulations.

Given that only the cardiovascular field was considered in this study, it is not possible to extrapolate the conclusions. In addition to the study mentioned above, other studies show a similar trend (see, for example, a report by the UK Biotechnology and Biological Sciences Research Council, and the recent scientific publication by Kahrass *et al*. and Del Pace *et al*. (19; 26; 27))). Nevertheless, it would be desirable to conduct a similar study in other research fields so that it can be seen whether the same findings emerge.

Monitoring the transition

A benchmarking instrument has been developed that can be used for reflexive monitoring of the transition in fundamental research (21). The Beyond Animal Testing Index (BATI) is a benchmarking instrument that provides an overview of efforts of knowledge institutions in research innovation and the transition to animal-free inno-

vation. In this way, organisations gain insight into their own progress, compare these insights with those of other organisations, and therefore learn from and encourage each other. To make it suitable for a specific research area, the BATI should include the various aspects of a target image and be able to measure its progress.

3.4 Education and training

At 3.0% of the total number of animal tests conducted in 2022 in the Netherlands (18), and 1.7% of the total in Europe (6), education and training is not the largest of the four domains. That said, education and training are crucial for systemic change and the transition to animal-free research within all the domains. Education forms the foundation for a new generation of stakeholders across the entire transition and supports the current generation in navigating the opportunities and challenges associated with the transition. Therefore, it is essential that current and future stakeholders become acquainted with the transition and feel connected to and engaged with the transition.

The transition goal or ambition

The NCad noted in its Transition Policy Advice 1.0 that there was sufficient potential for a significant reduction in the use of laboratory animals for education and training. The most concrete follow-up given to the recommendations concerning education and training is the target image for laboratory animal-free innovation in higher education (28). This target image was presented by the Universities of the Netherlands (UNL) and the Netherlands Federation of University Medical Centres (NFU) late 2022, with the objective of reducing the use of animals within the undergraduate and graduate education, and postgraduate continuing education for professionals. Amongst other things, this target image proposes modernising the laboratory animal science courses for researchers by expanding the theoretical part and including new approach methodologies) and innovations (thereby making these courses more relevant for master's students of biomedical sciences, biopharmaceutical sciences and biology, resulting in a new format that does not use live laboratory animals at all. The practical part of this only must be made available as more personalised courses for those who will be conducting animal experiments. This also touches on what some interviewees noted about the need for increased focus on education in animal-free innovations among established researchers as part of lifelong learning programmes.

Acceptance and implementation

Several interviewees noted that the next generation of researchers is already better informed about animal-free research and related technologies. Young researchers are increasingly becoming more critical about the inclusion of animal experiments in graduate and undergraduate curriculum. Some interviewees mentioned it as surprising that animal-based practicals are not at least optional nationwide, as this hinders a conscious choice for an animal-free research career. The curricula for study programmes and courses are based on predefined learning objectives. It is recommended to evaluate the learning objectives of the study programmes and courses and to adjust them where necessary. Given the international scope of research, it is important to also put animal-free education and training on the agenda internationally. It was partly for this purpose that the Global Education Hub was started on the initiative of TPI Utrecht and PETA UK.

4. Starting principles of Transition Policy Advice 1.0 revisited

4.1 Insights in the context of transformative governance

The Transition Policy Advice 1.0 used the 'Multi-Level Perspective' (MLP) as the starting point. The MLP identifies three levels: the niche-level or micro-level, where innovations are generated; the regime-level or meso-level, which is divided into sectors; and the landscape-level or macro-level, which encompasses society as a whole. The starting point of the consultations that ultimately led to the Transition Policy Advice 1.0 was that the changes and developments needed for landscape-level transition emerge from the micro-level and meso-level. The concept of transformative governance offers further insights to complement the MLP, and assumes that direct, widespread societal transformation is feasible. This stems from the realisation that fundamental changes are often not triggered from the regime itself, but by from outsiders (e.g., in the field of artificial intelligence) or societal pressure (landscape level). Changes within the regime often tend to be gradual rather than transformative. By recognising potential relationships between different transitions, transformative governance facilitates transformative solutions.

To assist in drafting the Transition Policy Advice 2.0, the NCad sought expert input from Radboud University, specifically from Prof. Ingrid Visseren-Hamakers, chair of the Environmental Governance and Politics group, and Rebecca van Eijden, who holds an MSc in Environment and Society Studies. For the expert input, the following questions were formulated: 1. How can the degree of implementation of the Transition Policy Advice 1.0 be interpreted from the transformative governance concept?; and 2. What insights does transformative governance offer for Transition Policy Advice 2.0? Prof. Ingrid Visseren-Hamakers and Rebecca van Eijden's expert input, including a description of transformative governance, is published in the form of a background document and was prepared independently of the NCad (29). The following is a factual summary of the key points of this expert input.

One finding is that the Transition Policy Advice 1.0 has been implemented only to a limited extent. Transformative governance suggests this could primarily be due to the involvement of regime actors who have been attempting to drive the transition within the existing paradigm, often using animal experiments as the starting point, whereas a genuine transition demands disruptive changes. In this context, disruptive change means that achieving the intended transition goal requires more than technological innovation alone. It also involves changes to other regime elements such as practices, behaviour, conceptual frameworks, infrastructure, and markets,

as well as regulation and policy (30). To summarise, regime actors operate within the established infrastructure and prevailing mores that underpin the existing regime. Generally speaking, because regime actors are chiefly involved, factors that favour gradual change currently outweigh those that help to initiate and accelerate the transition. Accordingly, the recommendation is to 'break open' the transition by including societal groups that, while not directly involved in research using animals, can still be considered stakeholders. Opening up the transition will amplify the voices of those whose interests are still largely overlooked, fostering a greater input and focus on society-wide aspects and the interplay of other transitions with the transition to animal-free research. It is necessary to reflect on existing paradigms, to understand how they either impede or actually stimulate the transition to animal-free research. One paradigm worthy of consideration in this regard is the economic paradigm of continuous growth that prioritises financial returns. Another is the paradigm that places human health and safety above all else. The principle of transformative governance underscores the importance of not always striving for consensus and of preventing the most resistant actors from dictating the transition's ambition or setting its pace. Hence, the government must have clear responsibilities in its leadership role, and the ministries must have sufficient capacity for leadership and implementation. The government should set its own goals, based on input from society.

A transition involves promoting desired developments or behaviours in pursuit of the ultimate goal, while at the same time curbing any that are unwanted. It has been observed that, following the Transition Policy Advice 1.0, the emphasis has mainly been on expanding animal-free innovations, with less regard being given to phasing out animal experiments. The Dutch Research Institute for Transitions (DRIFT) has developed the X curve, a visual tool that provides insight into these processes (see Figure 1).

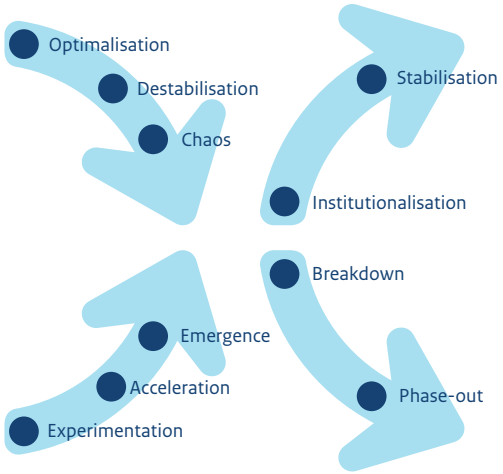

Figure 1. *The X curve of transitions. The X curve is a concept or framework that differentiates between patterns of expansion and phasing out, which can either complement or oppose one another. The figure is derived from a DRIFT publication entitled 'An actionable understanding of societal transitions: the X-curve framework' (31; 32).*

The recommendation from transformative governance is to formulate policies and initiatives that facilitate societal and political dialogue about the drawbacks and limitations of animal experiments, the urgent need for animal-free innovations, opportunities to prevent animal experimentation, and the usefulness and necessity of various animal experiments. These initiatives should make dominant values, such as the freedom of science or market forces, open to discussion. One tangible suggestion to facilitate the dialogue with the public is to establish a citizens' forum to question what the transition's intended ultimate goal is, what risks we are prepared to accept (from both animal experiments and animal-free innovations), what we want to phase out – even in the absence of alternatives, the societal issues we want to address, etc.

The concept of transformative governance emphasises the importance of formulating clear transition goals that offer a long-term outlook, also for companies and actors investing in the development, acceptance, validation, and implementation

of animal-free methods. The ambition expressed by the former State Secretary Van Dam in 2016 in his request for an opinion from the NCad, namely "the Netherlands should become a world leader in animal-free innovations by 2025", emphasised the urgent need for regime changes and for niche actors to step up and get involved in the transition. The NCad advised the minister to take control. The former Netherlands Ministry of Agriculture, Nature and Food Quality (LNV) implemented this through the partner programme Transition to Animal-Free Innovation (TPI), to which several relevant stakeholder parties were affiliated. From the perspective of transformative governance, there is a concern that, in this scenario, the ambition or speed of the transition is dictated by the actors most resistant to change. An important takeaway from other transitions is the need to set clear milestones in addition to the ultimate goal. This includes expanding activities that drive the transition and phasing out those that impede it, while identifying and utilising synergies between different transitions. Setting milestones is vital for shaping the ambition and pace of the transition. Consider the energy transition, for example, where the ultimate goal is to be fully climate-neutral by 2050, with clear milestones such as a '55% reduction in emissions by 2030' and phasing out fossil fuel subsidies. The phasing out of activities should be facilitated and fair, for example, by means of grants for training in animal-free research, interdisciplinary collaboration, as well as developing, implementing, and ensuring access to animal-free innovations.

When formulating policy, it is essential to consider all pertinent transitions and policy areas (e.g. climate and energy, biodiversity, agriculture, health, mobility, circular economy) to avoid negative interactions, encourage synergies, and find opportunities to accelerate one transition through another. The formulation of a national strategy should be complemented by an international strategy, to achieve the set goals. Starting with the EU and its institutions, leverage their relationships with similar institutions worldwide to expand the network. Finally, a system of learning evaluation is required to track the transition's progress. Based on this, the NCad could periodically update its Transition Policy Advice with the latest insights on what is required each year to accelerate the transition.

4.2 Perspectives on human-animal relations

The concept of transformative governance highlights the interests of animals as an under-recognized value in this transition, while in essence, the transition not only aims to improve research quality and translational value, but should also serves the interests of animals. Partly for this reason, the NCad sought expert input regarding the latest trends in human-animal relations from Dr Koen Kramer (Utrecht University) and Dr Bernice Bovenkerk (Wageningen University & Research), with assistance from committee member Katja ten Cate. The background document prepared by these experts is published on the NCad website (33). A factual summary of this is included here.

The underlying normative (and, by derivation, legal) standpoint in many animal procedures is the belief that the interests of animals are subordinate to those of humans. After all, the lives and welfare of animals are sacrificed to improve human health and welfare, for example. This normative standpoint is rooted in the belief that there are morally significant differences between humans and animals. The arguments typically put forward to support this belief are that, unlike humans, animals have little or no self-awareness, language, culture, and/or cognitive abilities. Accordingly, humans have a higher moral status than animals.
Nevertheless, advances in the study of ethology, particularly comparative cognitive ethology, are constantly adding to our understanding of animals' capabilities, necessitating a reassessment of this notion. Animals can suffer, just like humans. They also exhibit communication skills (some even have language), intentional behaviour, unique personalities, cultural traits, and even a sense of fairness.
This new understanding reshapes our view of animals, of what is important for them, and of whether our treatment of them can be justified. As a result, this new understanding also impacts considerations about whether, and under what circumstances, animal experiments can be justified.

In the light of this new understanding of animals' capabilities, we can no longer define what is important for them purely in terms of the absence of discomfort, such as pain, distress, or stress. That would be too narrow an interpretation of welfare. We now understand that proper welfare also involves enabling animals to display social and natural behaviour, make choices, have some degree of control over their circumstances, and attain a positive emotional state. In animal ethics, new ethical concepts have emerged that go 'beyond welfare' – ideas deemed relevant to ethical interactions with animals, but which are not necessarily directly related to their welfare. These concepts include *integrity*, *agency*, *instrumentalisation*, and *telos*. These concepts were developed to better address and balance the interests of animals. The report, which is published as a background document, details the trends in

animal ethics and the concepts currently being employed in that context. The existing assessment framework for evaluating the moral acceptability of animal experiments makes little or no practical use of these concepts.

If we take current trends in scientific knowledge about animals and developments in animal ethics seriously, we need to set more stringent standards for justifying the use of animals than we have in the past, if such justification is even possible today.

4.3 Harms-benefit analysis (ethical assessment)[8]

In fundamental research, scientific freedom is a key value that is associated with the responsibility to think critically. When conducting fundamental research with animals, the importance of scientific freedom and the acquisition of new knowledge are weighed against the interests of the animals through the legally mandated harms-benefit analysis, also known as the ethical review. The NCad requested expert input from Dr Koen Kramer (Utrecht University) and Dr Bernice Bovenkerk (Wageningen University & Research), with assistance from committee member Katja ten Cate, on how fundamental scientific research with animals should be ethically assessed. The report prepared by these experts has been published as a background document to this evaluation (34). The following is a factual summary of that report.

Upon closer inspection of the current assessment framework, we are forced to conclude that, on one side of the scale, animal welfare is narrowly understood as merely the absence of distress, while other key aspects like integrity, agency, and telos are still largely overlooked (even though recent ethological findings should compel us to do better). On the other hand, determining the benefits of animal experiments presents the greatest possible challenges. When it comes to fundamental scientific research, the type of research in which most laboratory animals are used, this turns out to be virtually impossible. In his report, Dr Kramer points out various uncertainties and ambiguities that arise when performing a harms-benefit analysis for fundamental scientific research, as required by law.

[8] The NCad prefers the term harms-benefit analysis (instead of harm-benefit analysis) because animal procedures can inflict harm in various ways, in terms of its nature, severity, and extent. The term 'harms' more effectively captures the impact on individual animals used in experiments, animals bred but not used, and the staff working with these animals, etc.

Dr Kramer provides examples to demonstrate and explain the presence of various types of uncertainty in fundamental research, ultimately concluding that a reliable harms-benefit analysis is not feasible, even with different decision rules than those used in a standard harms-benefit analysis.

The developments and bottlenecks identified above all support the conclusion that the current ethical assessment framework is inadequate, prompting the NCad to reconsider the moral acceptability of animal procedures and the ethical assessment framework used for this purpose in everyday practice.

4.4 Funding flows

In its Transition Policy Advice 1.0, the NCad advised the government to prioritise funding for animal-free innovations. The sections below summarise the general state of affairs in the EU and the Netherlands. To this end, the NCad made use of two reports by The Business Research Company (35; 36), a market research company, included as background documents to this evaluation, along with a 2020 report by Technopolis Group (37), a research and consultancy firm. This information has been supplemented with desk research and expert input from the NCad. The amounts and percentages shown in the cited source documents are estimates. In reality, it turns out to be very challenging to obtain a clear picture of this information, partly because funding is not explicitly allocated for research with animals, but for specific research questions, which may or may not involve research with animals. Hence, the data presented in these reports should be regarded as rough indications.

The Business Research Company defines the 'market for scientific research with animals' as the total costs incurred by end users, including academia, industry, and CROs, who use animals to test their products. These costs cover the purchase and upkeep of animals, but do not include breeding costs. The 'market for animal-free methods' is defined as the total costs incurred by end users, including academia, industry, and CROs, who use alternative methods instead of animals to test their products. These costs cover the purchase of the necessary technology and any additional operational expenses.

According to the Business Research Company's analysis, in 2019, an estimated $10.74 billion was spent globally on scientific research involving the use of animals. The forecast for the subsequent years indicates a modest level of growth that will

slowly stagnate. According to the cited source reports, this stagnation in scientific research with animals is due to the high costs of animal experiments, institutional or corporate demands to implement the 3R principle, stricter regulations, ethical concerns about animal experiments, a growing preference among end-user industries for adopting animal-free testing technologies to bring them more into line with consumer preferences, and the emergence of animal-free innovations.

According to the Business Research Company, in 2019, $1.11 billion was spent globally on animal-free methods. Despite much lower investment in animal-free methods, the growth rate here is expected to be roughly twice as much as research using animal. This expected increase is partly due to the growing acceptance of *in vitro* cell and tissue cultures, organs-on-chips, computer simulations, 3D bioprinted tissues, and synthetic skin substitute technology particularly by the industrial sector.

Western Europe is the world's third-largest investor in animal-free methods, after the United States and Japan. From a financial perspective, cell culture technology is currently the most rapidly expanding technology in the field of animal-free methods.

Developments in Western Europe

In response to increasing appeals from the European Parliament, EU agencies, members of the public, academics, and industry for a transition to more biologically relevant animal-free approaches, the European Commission implemented a number of specific measures in 2023. The Commission is currently formulating a roadmap to phase out the use of animals in chemical safety assessments and is looking into a potential policy action from the forthcoming European Research Area (ERA)[9] to fast-track the development, validation, and acceptance of animal-free approaches in biomedical research and pharmaceutical product testing.

Furthermore, two calls have been launched as part of the Horizon Europe programme to accelerate the development and use of human models.[10] On the other hand, however, a funding option specifically targeting laboratory animal research has been introduced.[11] The Innovative Health Initiative, an EU public-private partnership, launched a similar call in 2023, designed to fast-track the implementation of animal-free methods.[12]

Over the past few years, various European nations have revealed plans to reduce and replace the use of animals in scientific research and educational settings. In 2021, the Flemish Parliament set in motion a project to devise an action plan aimed at reducing the use of animals for scientific purposes (38). Following wide-ranging round table discussions with 20 organisations connected to the Flemish initiative, these groups have proposed 33 individual actions, all focused on reducing animal procedures.

Furthermore, the Brussels Animal Welfare Code will feature a section on the use of animals for scientific purposes, in line with Directive 2010/63/EU. This sets out a five-year strategy for reducing animal experiments, incorporating steps to advance animal-free approaches and foster inter-regional and supranational cooperation. Additionally, a priority-based action plan will be devised to progress towards the ultimate goal of fully replacing animal models.

In February 2024, the United Kingdom announced that a plan would be published by the following summer to accelerate the development, validation, and acceptance of alternative methods to replace the use of animals in scientific research.[13]

[9] The European Commission made these pledges in its response to the European Citizens' Initiative 'Save Cruelty Free Cosmetics - Commit to a Europe Without Animal Testing'.https://single-market-economy.ec.europa.eu/publications/communication-commission-european-citizens-initiative-eci-save-cruelty-free-cosmetics-commit-europe_en

[10] Horizon call HORIZON-HLTH-2024-IND-06-09: Gaining experience and confidence in New Approach Methodologies (NAMs) for regulatory safety and efficacy testing – coordinated training and experience exchange for regulators and Horizon call HORIZON-HLTH-2024-TOOL-05-06-two-stage: Innovative non-animal human-based tools and strategies for biomedical research

[11] Horizon call HORIZON-JU-IHI-2023-04-01-two-stage: Expanding translational knowledge in minipigs: a path to reduce and replace non-human primates in non-clinical safety assessment

[12] Horizon call HORIZON-JU-IHI-2023-05-01: Accelerating the implementation of New Approach Methodologies and other innovative non-animal approaches for the development, testing and production of health technologies

[13] The British Minister of Science made this pledge during a debate on animal procedures. The transcript of that debate has been published at: https://www.animalfreeresearchuk.org/westminster-hall-debate-february-2024/

In 2021, the German federal government declared its intention to devise a strategy to reduce the number of animal experiments and allocated €2 million for the development and implementation of that strategy in 2023.

These cases all demonstrate that both the level of the EU and its Member States there is increasing investment in animal-free innovations.

Developments in the Netherlands

In 2020, the Technopolis Group, a research and consultancy firm, conducted a study (37) into the proportion of public funding for animal-based research compared to government spending on animal-free innovations in laboratory animal centres. This study revealed that the majority of government funding is still being allocated to research with animals. The estimated total public expenditure on fundamental scientific research with animals for the reference year 2018 was €50-60 million. For the reference year 2018, government funding for the development and/or application of animal-free innovations was estimated at €20-35 million. These figures are rough estimates. According to the Technopolis Group, there is a lack of insight into the public funding of animal experiments and animal-free innovations. Uniform reporting (or a uniform reporting requirement) is essential if the government is to manage investments effectively. In line with the Transition Policy Advice 1.0, the period leading up to this evaluation has seen a steadily increasing focus on pathway funding and on the involvement of private parties as clients and/or funding bodies, or as providers of in-kind support. An example is the Netherlands Organisation for Health Research and Development's (ZonMw) grant programme More Knowledge with Fewer Animals (MKMD), which includes the Create2Solve initiative. While this funding has increased, it still falls short of what is needed to ultimately achieve the transition. It is worrying that the budget is insufficient to honour all the projects that are relevant and assessed as at least good.

In recent years, several grants have been awarded that can be earmarked for the development, validation, acceptance and implementation of animal-free innovations. A few notable examples are listed below.

In March 2021, the Dutch Research Council (NWO) announced a €3.4 million ($4.0 million) grant for the organs-on-chips being developed by the hDMT consortium, which is made up of various research groups, companies, and knowledge institutions, including the Dutch Society for the Replacement of Animal Testing. This consortium is working to establish a universal standard for organs-on-chips, with the goal of connecting several organs-on-chips to simulate a complete body. The consortium itself is investing €1.4 million in the project.

In 2021, the NWO domain Applied and Engineering Sciences (AES) , the Association of Collaborating Health Foundations (SGF), ZonMw, and the Top Sector Life Sciences & Health (LSH; HealthHolland) jointly allocated €5.55 million for the development and validation of human measurement models. The Dutch Society for the Replacement of Animal Testing (in Dutch: Stichting Proefdiervrij) also supports projects within this programme. Two rounds of funding have led to the approval of 13 projects, with over €9 million in research grants made available. A new call for grant applications for research into human measurement models has now been opened for 2024, providing €5.4 million in funding.

In 2023, the European 'Partnership for the Assessment of Risks from Chemicals' (PARC) was launched, with a total budget exceeding €400 million. Various ministries in the Netherlands are providing substantive support and funding. In the Netherlands, PARC is managed by the National Institute for Public Health and the Environment (RIVM), with as partners the Vrije Universiteit Amsterdam (VU), Utrecht University - Institute for Risk Assessment Sciences (UU-IRAS), the Netherlands Organisation for Applied Scientific Research (TNO), Wageningen University & Research (WUR), Wageningen Food Safety Research (WFSR), Radboud University Medical Center (Radboudumc), Leiden University, and the KWR Water Research Institute (KWR). PARC is committed to advancing knowledge to improve the efficiency and effectiveness of chemical and product risk assessments, with a focus on animal-free innovations.

In March 2024, it was announced that the National Growth Fund is investing €125 million in a new Centre for Animal-Free Biomedical Translation (CPBT). These are significant developments. However, additional steps will be needed to stimulate the transition to animal-free research and education across all fronts. It will be necessary to identify any supplementary funding options that have previously been overlooked. Valuable insights could be gained from public-private partnerships in other transition and innovation projects with similar risk profiles.

5. Findings and starting points for the Transition Policy Advice 2.0

The objective of this evaluation is to review the progress of the transition to animal-free research and the impact of the Transition Policy Advice 1.0. This evaluation draws on interviews conducted with national and international representatives of stakeholder groups. New insights into human-animal relationships and the harms-benefit analysis and perspectives from transformative governance, make it necessary to revisit the starting points of the Transition Policy Advice 1.0. Drawing on the evaluation and the results of the performed projects, the NCad comes to the following findings and concepts as relevant input for the next 'Transition Policy Advice' and the wider debate on research with animals.

5.1 General findings and groundwork for the Transition Policy Advice 2.0

The evaluation indicates that the transition is progressing steadily, both in the Netherlands and internationally, with changes taking place in all domains of scientific research. This is also evident in the evolving regime and landscape, where animal-free research has gained a more prominent status.

At the same time, the NCad observes that the current focus is still largely on the development and implementation of animal-free innovations. Approaches such as reshaping or phasing out certain activities by changing behaviour, for example, or designating research to be phased out, remain largely overlooked. Society requires science to use not only the best model but also the one that is most ethically sound. The focus on innovation is evident in the goal as usually formulated for this transition, namely the 'transition to animal-free research' or the 'transition to animal-free innovations', and in the predominantly scientific involvement and initiatives. Consequently, the transition is now being mainly driven by technical considerations, which, while essential, are not sufficient to achieve and justify the transition. One way to give the transition greater momentum is to actively involve the societal community, including citizens, patients, and consumers. In light of recent findings about animals' capabilities, it is only right to further articulate and advocate a new vision of the human-animal relationship and, consequently, the ethical responsible use of animals. Current considerations give insufficient weight to their interests. Involving a wider range of stakeholders in the transition ensures that, alongside the technical aspect, other elements such as social and ethical considerations are addressed. A key feature of any transition process is the combined focus on social, technical, and institutional aspects, including ethics and standard setting (39).

A stronger focus on these aspects is vital in pursuing the ultimate goal of the worldwide transition – a society without animal experiments.

Although it is unclear if and when a society entirely without animal testing can be achieved, especially given the international context, pursuing transformation demands an ambitious and clearly formulated target, even when there is uncertainty and ambiguity among stakeholders about its feasibility. For this reason, the NCad speaks of striving for a society without animal experiments.

In the transition to a society without animal experiments, it is vital that stakeholders in research with animals and research into technological innovations feel (or continue to feel) engaged and to take ownership, and work towards animal-free solutions to research questions. The results of this evaluation imply that, in practice, transition initiatives are typically pursued within existing systems and structures. The NCad underscores the importance of thinking from the perspective of the target organism, while considering the relevance (including societal relevance) and nature of the research question. These standpoints should be key factors in advancing the development and implementation of animal-free innovations and in expediting the reshaping of existing systems and structures. In addition, the "valley of death" continues to be a major hurdle. It is important to explore what resources are required to progress animal-free innovations from the development phase to validation, acceptance, and implementation, and what opportunities can be created with multidisciplinary, public-private, and international collaborations.

The government is the only stakeholder with the right tools to take on a robust and strategic leadership role. For the transition to gain traction and succeed, it is essential that the government adopts a directing or directive role, taking the initiative in setting frameworks and goals. Cooperation and ownership among all parties is thereby essential. The Ministry of LNV (now LVVN) is currently fulfilling the leadership role in this transition by focusing on connecting and facilitating efforts through the partner programme TPI. The NCad notes that there is currently no clear transition strategy, yet this is essential to harness and channel the attention and energy of professionals in the field and of society as a whole. Additionally, there is overlap in both values and stakeholders of this transition with other transitions including societal transitions, Such as the transition to a healthy living environment, circular agriculture and sustainable food systems, and the transition to a future-proof healthcare system. As a result of this overlap, transitions can either augment or impede one another. Coordinating policies across all interconnected transitions may offer added value, since inter-ministerial cooperation is key to develop integrated and sustainable solutions.

In the Transition Policy Advice 1.0, the NCad set the transition's course with domain-specific recommendations. However, it seems that the focus has generally shifted towards the former State Secretary's ultimate goal of "the Netherlands becoming a world leader in animal-free innovations by 2025". Furthermore, one key finding of this evaluation is that the essential and more concrete definition of the transition's ultimate goal, along with the necessary tools, which must include funding, has not yet been adequately addressed. The NCad feels that subdividing the transition into segments with specific milestones across different domains and timelines helps to drive the transition forward. These milestones should be given new and concrete content.

This evaluation indicates that the transition's progress is not yet being effectively monitored. In its leadership role, the government needs effective monitoring to identify bottlenecks early, take timely action, and fulfil its role efficiently (whether through coordination, facilitation, or leadership). A system of learning evaluations is needed, where progress is continuously assessed against clear intermediate goals, involving more than the number of animal experiments. It is important to focus guidance not only on 'what' is being done, but also on 'how' it is being done, and by 'whom'. The transition to a society without animal experiments has many similarities with the technical, social, and ethical dimensions of other transitions, for example in terms of target groups, conflicting interests, and the availability of or need for innovations. Accordingly, the monitoring instruments already in place for other transitions, such as those for the energy transition, should be reviewed to determine their individual suitability. It is also important to consider what can be learned from other transitions for the transition towards a society without animal experiments, for example in terms of managing resistance, leveraging opportunities, and the vision needed to achieve long-term goals.

5.2 Efficacy and safety testing

This evaluation suggests that, compared to other domains in which animals are used in scientific research, a substantial number of national and international initiatives have been initiated that are associated with the transition to animal-free efficacy and safety testing. In some cases these involve large-scale multidisciplinary collaborations and there are also examples where initiatives are linked to concrete sub-goals. These trends suggest that momentum is building. However, the NCad notes that the government has not formulated or disclosed any international strategy or cooperation agenda with other Member States and key European and international organisations. Aside from the technological and ethical considerations, it is the social and legal aspects that are particularly relevant to the transition within this domain. Care must be taken to ensure that the uncertainty experienced with animal-free innovations and, to a lesser degree, with research with animals, does not impede or even negate the progress that has already been made. This calls for a different approach to real versus perceived risks and makes it necessary to have a focus on creating synergies and pinpointing bottlenecks between various European laws and regulations, and between these and non-European policies. The NCad therefore notes that significant progress in phasing out research with animals in this domain can only be achieved by focusing on paradigm shifts in regulatory research.

5.3 Fundamental scientific and translational research

Fundamental research is the cradle of innovation and is key to the transition towards a society without animal experiments. As translation faces insurmountable limitations, a growing number of researchers are shifting their focus – partially or entirely – to the development or potential of existing animal-free techniques. Animal-free research is now mainly regarded as complementary to research with animals, since animal-free methods mainly tend to answer different questions than those explored using with animals. The long-standing research practices are proving difficult to change and have prompted many initiatives to focus on optimising existing systems. This strategy is insufficient to bring about the transition. The NCad recognises the need for additional strategies alongside the development of animal-free innovations, placing greater emphasis on the interests of society and ethics (informed by new insights into the interests of animals) when considering the use of animals in research, so that animal-free research is more explicitly the starting point and target. Engaging and coordinating with international initiatives, such as the upcoming ERA policy action and grant programmes like Horizon Europe, present opportunities to stimulate further progress towards a society without animal experiments.
The "harms-benefit analysis" project highlights many bottlenecks in performing this analysis for fundamental scientific research, concluding that this can in fact not be done in a way that does justice to the interests of animals. The NCad recognises the need to identify these bottlenecks and to engage with stakeholders to recalibrate the ethical assessment framework, especially in the context of fundamental scientific research. The NCad concludes that the target images provide an effective model for identifying opportunities within areas of fundamental scientific research. The target images also highlight the challenge of balancing ambitious, groundbreaking goals with a realistic pathway that includes tangible sub-goals that can move the field forward. So far, however, the involvement of the social and societal field in shaping these target images has been minimal or non-existent. As a result, the issue of their societal relevance have not been fully explored. Furthermore, some of the target images are insufficiently ambitious and fail to fully address the question of how the transition can be shaped. In addition, there is no clear plan for the implementation and development of the target images. To follow up on this instrument, it is advisable to explore the boundary conditions within which the realisation of a target image possible. This could include the involvement of societal and ethical considerations, establishing links with and taking ownership of clear sub-goals, securing resources to achieve these sub-goals, and monitoring progress.

5.4 Education and training

The sub-transition within the domain of education and training concerns both current and future generations of scientists and educators and is an essential catalyst for the transition to animal-free research across all areas of research. Several initiatives have been launched within this domain, including the target image for *innovation in higher education using fewer laboratory animals*, owned by the Universities of the Netherlands (UNL) and the Netherlands Federation of University Medical Centres (NFU), and the establishment of the Young TPI network. However, it remains uncertain whether these developments will fully permeate the field and lead to changes in both educational programmes and laboratory best practices. By implementing a coordinated strategy and robust monitoring, momentum can be generated to ensure these initiatives are embraced by all stakeholders across the Netherlands, with the principles firmly embedded in programmes' curricula, courses, and apprenticeships. Given the international nature of research, it's essential to promote these initiatives on an international scale.

References

1. Think Tank on Supplementary Financing for Alternatives to Animal Procedures. In transition! The Netherlands leads the way in innovations without laboratory animals [Denktank Aanvullende Financiering alternatieven voor dierproeven, in opdracht van het Ministerie van Economische Zaken Oktober 2015. In transitie! Nederland internationaal toonaangevend in proefdiervrije innovaties]. [only in Dutch] The Hague, the Netherlands, 2015. https://www.transitieproefdiervrijeinnovatie.nl/documenten/rapporten/15/10/15/in-transitie

2. Geels, F.W. Technological transitions as evolutionary reconfiguration processes: a multi-level perspective and a case-study. Research Policy. 2002, Vol. 31, pp. 1257-1274. https://doi.org/10.1016/S0048-7333(02)00062-8

3. IPSOS. Public attitudes to animal research in 2018. 2019. https://www.ipsos.com/en-uk/public-attitudes-animal-research-2018

4. European Citizens' Initiative - Save Cruelty Free Cosmetics - Commit to a Europe Without Animal Testing. 2023. https://citizens-initiative.europa.eu/save-cruelty-free-cosmetics-commit-europe-without-animal-testing_en

5. European Citizens' Initiative - Stop vivisection - Commission registration number: ECI(2012)000007. 2013. https://citizens-initiative.europa.eu/initiatives/details/2012/000007_en

6. European Commission. ALURES – ANIMAL USE REPORTING - EU SYSTEM EU STATISTICS DATABASE ON THE USE OF ANIMALS FOR SCIENTIFIC PURPOSES UNDER DIRECTIVE 2010/63/EU. https://webgate.ec.europa.eu/envdataportal/content/alures/section1_number-of-animals.html

7. RIVM. Roadmap for animal-free innovations in regulatory safety assessment. 2018. https://www.rivm.nl/en/documenten/roadmap-animal-free-innovations-in-regulatory-safety-assessment

8. Government of Canada. Bill S-5: Strengthening Environmental Protection for a Healthier Canada Act. 2023. https://www.canada.ca/en/environment-climate-change/news/2023/06/bill-s-5-strengthening-environmental-protection-for-a-healthier-canada-act.html

9. U.S. EPA. U.S. EPA Holds Inaugural Conference on Reducing Animal Testing for Chemical Safety. December 2019. https://www.epa.gov/newsreleases/us-epa-holds-inaugural-conference-reducing-animal-testing-chemical-safety

10. European Commission: Directorate-General for Internal Market, Industry, Entrepreneurship and SMEs and Cronin, M., Report of the European Commission workshop on "The Roadmap Towards Phasing Out Animal Testing for Chemical Safety Assessments" – Brussels, 11-12 December 2023, Publications Office of the European Union, 2024, https://data.europa.eu/doi/10.2873/34576

11. NWO. Thematic programme of the Dutch Research Agenda (NWA) - Animal-free assessment models: acceptance and implementation. 2021. https://www.nwo.nl/en/researchprogrammes/dutch-research-agenda-nwa/thematic-programming/animal-free-assessment-models-acceptance-and-implementation

12. Kienhuis, A, de Wit-Bos, L and van Engelen, J. 'New approach Methodologies in the safety assessment of consumer products and food. ['New Approach Methodologies' in de veiligheidsbeoordeling van consumentenproducten en voedsel.] [only in Dutch] RIVM, 2020. RIVM-briefrapport 2020-0093. https://www.rivm.nl/publicaties/new-approach-methodologies-in-veiligheidsbeoordeling-van-consumentenproducten-en

13. ZonMw. Knowledge Agenda on the Transition to Non-Animal Innovations. [Kennisagenda. Transitie naar Proefdiervrij Innovaties] [summary available in English] 2023. https://www.zonmw.nl/en/knowledge-agenda-transition-non-animal-innovations#:~:text=The%20Knowledge%20Agenda%20on%20the,introduction%20of%20non%2Danimal%20innovations.

14. Ministry of Agriculture, Nature and Food Quality (LNV). Parliamentary letter on progress on Transition to Animal-Free Innovation [Kamerbrief over voortgang Transitie Proefdiervrije Innovatie] [only in Dutch]. 2020. https://open.overheid.nl/Details/ronl-c923b15d-bdb3-44d7-8afc-ec2c3c5e2848/1?hit=1&text=DGA-DAD+%2F+20138534#panel-gegevens

15. European Commission. Special Eurobarometer 550: Attitudes of Europeans towards the environment. 2024. https://europa.eu/eurobarometer/surveys/detail/3173

16. ECHA. The use of alternatives to testing on animals for the REACH Regulation. Fifth report under Article 117(3) of the REACH Regulation. 2023. https://echa.europa.eu/nl/animal-testing-under-reach

17. Zuang, V., Barroso, J., Berggren, E., Bopp, S., Bridio, S., Casati, S., Corvi, R., Deceuninck, P., Franco, A., Gastaldello, A., Langezaal, I., Malinowska, J., Mennecozzi, M., Milcamps, A., Munn, S., Piergiovanni, M., Prieto-Peraita, P., Sampani, S., Valsesia, D., Whelan, M., Wittwehr, C. and Worth, A., Non-Animal Methods in Science and Regulation, Publications Office of the European Union, Luxembourg, 2024, doi:10.2760/05390, JRC136460.

18. NVWA. Annual overview of animal experiments and laboratory animals ('Zo doende') 2022, by the Dutch Food and Consumer Product Safety Authority (NVWA) [Zo doende 2022. Jaaroverzicht dierproeven en proefdieren van de Nederlandse Voedsel- en Nederlandse Voedsel- en Warenautoriteit]. [only in Dutch] 2024. https://www.nvwa.nl/documenten/dier/dierenwelzijn/zo-doende/publicaties/zo-doende-2022-jaaroverzicht

19. BBSRC, Biotechnology and Biological Sciences Research Council. BBSRC survey report on the use of models in research. 2022. https://www.ukri.org/publications/bbsrc-survey-report-on-the-use-of-models-in-research/

20. Krebs, C.E., et al. A survey to assess animal methods bias in scientific publishing. ALTEX - Alternatives to animal experimentation. 2023, Vol. 40, 4. https://doi.org/10.14573/altex.2210212

21. Krul, C, et al. Beyond Animal Testing Index: Benchmarking tool for a world beyond animal testing. ALTEX - Alternatives to animal experimentation. 41, 2024, Vol. 1, pp. 69-75. https://doi.org/10.14573/altex.2304161

22. ECVAM, EURL. Biomedical research - Review of advanced non-animal models in biomedical research. https://joint-research-centre.ec.europa.eu/eu-reference-laboratory-alternatives-animal-testing-eurl-ecvam/biomedical-research_en. https://joint-research-centre.ec.europa.eu/eu-referencelaboratory-alternatives-animal-testing-eurl-ecvam/biomedical-research_en

23. Wieschowski, S, et al. Publication rates in animal research. Extent and characteristics of published and non-published animal studies followed up at two German university medical centres. PLoS ONE. 2019, Vol. 14, 11. https://doi.org/10.1371/journal.pone.0223758

24. ATMP letter 2023. Annex to Parliament letter on stimulating innovative drug development. [Bijlage bij Kamerbrief over stimuleren innovatieve geneesmiddelenontwikkeling]. [only in Dutch] 2023. https://www.rijksoverheid.nl/documenten/publicaties/2023/12/19/atmp-brief-2023

25. Inspire to Act. Exploratory study on the rationale and driver influencing methodological choices. Background document to this evaluation. 2023. https://www.ncadierproevenbeleid.nl/

26. Kahrass, H., Pietschmann, I. and Mertz, M. Why do I choose an animal model or an alternative method in basic and preclinical research? A spectrum of reasons and their ethical evaluation. Animals : an open access journal from MDPI. 4, 2023, Vol. 14, p. 651. https://doi.org/10.3390/ani14040651

27. Del Pace, L., Viviani, L. and Straccia, M. Researchers and Their Experimental Models: A Pilot Survey in the Context of the European Union Health and Life Science Research. Animals : an open access journal from MDPI. 20, 2022, Vol. 12, p. 2778. https://doi.org/10.3390/ani12202778

28. Universities of the Netherlands (UNL) and the Netherlands Federation of University Medical Centres (NFU). Ambition statement on innovation in higher education using fewer laboratory animals. 2022. https://www.ncadierproevenbeleid.nl/documenten/publicatie/23/2/22/ambition-statement-on-innovation-in-higher-education-using-fewer-laboratory-animals

29. Visseren-Hamakers, I and van Eijden, R. Transformative governance and transitions. Background document to this evaluation. 2023. https://www.ncadierproevenbeleid.nl/

30. Kivimaa, P, et al. Moving beyond disruptive innovation: A review of disruption in sustainability transitions. Environmental Innovation and Societal Transitions. 38, 2021, pp. 110-126. https://doi.org/10.1016/j.eist.2020.12.001

31. Diercks, G, et al. Steering in transitions: A framework for strategizing. [Sturing in transities: Een raamwerk voor strategiebepaling] [Only in Dutch] Drift for transition, 2020. https://drift.eur.nl/en/publications/sturing-in-transities-een-raamwerk-voor-strategiebepaling/

32. Hebinck, A, et al. An actionable understanding of societal transitions: the X-curve framework. 17, 2022, Vol. 3. https://doi.org/10.1007/s11625-021-01084-w

33. Kramer, K, Bovenkerk, B and Ten Cate, K. Progress in academic animal ethics and its relevance to the discourse on the use of animals in scientific research. Background document to this evaluation. 2023. https://www.ncadierproevenbeleid.nl/

34. Kramer, K and Bovenkerk, B. Project assessment in fundamental scientific animal research: is a harms-benefit analysis the best model? Background document to this evaluation. 2023. https://www.ncadierproevenbeleid.nl/

35. The Business Research Company. Non-Animal Alternatives Testing Global Market Opportunities And Strategies To 2030: COVID-19 Impact And Recovery. Achtergronddocument bij deze evaluatie. Background document to this evaluation. 2023. https://www.ncadierproevenbeleid.nl/

36. The Business Research Company. Animal Testing And Non-Animal Alternative Testing Global Market Opportunities And Strategies To 2035. Achtergronddocument bij deze evaluatie. Background document to this evaluation. 2023. https://www.ncadierproevenbeleid.nl/

37. Ploeg, M., et al. Study into the finances of animal testing and animal-free research innovations. [Studie naar de financiën van proefdieronderzoek en dierproefvrije innovaties]. [only in Dutch] technopolis group, 2020. https://www.technopolis-group.com/report/study-into-the-finances-of-animal-testing-and-animal-free-research-innovations/

38. Schrijver, L, Nooijen, A and Bastiaanssen, V. Action plan to reduce animal testing in Flanders [Actieplan. Gericht op het verminderen van het aantal dierproeven in Vlaanderen.] [only in Dutch] Technopolis group, 2023. https://www.technopolis-group.com/report/action-plan-to-reduce-animal-testing-in-flanders/#:~:text=In%202021%2C%20Animal%20Welfare%20Flanders,for%20reduction%20during%20roundtable%20discussions

39. Loorbach, D, Frantzeskaki, N and Avelino, F. Sustainability Transitions Research: Transforming Science and Practice for Societal Change. Annual Review of Environment and Resources. 42, 2017, Vol. 1. https://doi.org/10.1146/annurev-environ-102014-021340

Appendix A: Recommendations in the NCad opinion 'Transition to non-animal research' published in 2016

Clear transition objectives – The NCad recommends the following:

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 of 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 of 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 of 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 severala 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.

Appendix B: List of interviewees

Also for this evaluation, the NCad has gratefully made use of input from stakeholders and experts from the Netherlands and from abroad. Those consulted are not co-authors of this evaluation, and may hold opinions on certain points that differ from those presented by the NCad in this evaluation.

Chapter 3 of this evaluation was prepared based on interviews with the following individuals:

- Dr. Anne Kienhuis (RIVM, UU)
- Dr. Erica van Oort (former ZonMw)
- Dr. Imke Kross (former MSD Animal Health)
- Dr. Jan Lund Ottesen (Novo Nordisk; Danish 3R-Center)
- Prof. dr. Joop van Gerven (Central Committee on Research Involving Human Subjects (CCMO))
- Prof. dr. Judith Homberg (Radboud UMC)
- Dr. Kirsty Reid (EFPIA)
- Drs. Lennert Schrader (Netherlands Food and Consumer Product Safety Authority, NVWA)
- Drs. Lisette Krul (Association of Health Funds (SGF))
- Dr. Martijn Nolte (ZonMw)
- Dr. Peter Bertens (Vereniging Innovatieve Geneesmiddelen (VIG))
- Dr. ing. Peter van Meer (Medicines Evaluation Board (CBG))
- Drs. Reineke Hameleers (Eurogroup for Animals; NCad)
- Saskia Aan, MSc (former Stichting Proefdiervrij)
- Em. Prof. dr. Vera Rogiers (Mirror group European Partnership for Alternative Approaches to Animal Testing (EPAA)
- Dr. Victoria de Leeuw (Young TPI)
- Prof. dr. ir. Wiebe Bijker (former chair commitee 'target images animal-free innovation – neuroscience' from the KNAW)
- Drs. Wilbert Frieling, veterinarian (Charles River)
- Prof. dr. Wouter Dhert (Utrecht University)
- LNV policy officer TPI
- LNV policy officer animal testing

Note: On request, the names of some individuals have been omitted, and only the position has been mentioned.

Chapter 4 of this evaluation was prepared with contributions from the following experts:

- Prof. dr. Ingrid Visseren-Hamakers
- Rebecca van Eijden, MSc
- Dr. Bernice Bovenkerk
- Dr. Koen Kramer

Appendix C: Detailed description of the research strategy

The evaluation started with a series of interviews with national and international experts from the various disciplines who are directly or indirectly involved in conducting research using animals and the scientific or social debate on the subject. The central topic in these interviews was Transition Policy advice 1.0. However, the transition to animal-free research is complex and dynamic in nature as it touches on several national and international developments, such as in scientific innovations, research culture, legislation, and societal perceptions of scientific research. For this reason, the evaluation was conducted with an overarching approach, taking into account the full spectrum of the transition to animal-free research in the Netherlands. This approach allows for the synergy that has arisen in practice between the Transition Policy advice 1.0 and other developments.

Interviews

For this evaluation, experts and stakeholders were consulted regarding the transition to animal-free research in the Netherlands. The NCad reached out to participants from various stakeholder groups for the interviews, aiming to have – to the extent possible – a comprehensive representation of the various organisations and players in the field (see Appendix B).

The interviews were conducted in a semi-structured manner, allowing unanticipated topics to be discussed, and were carried out in two rounds. In the first round, eight individuals were interviewed with the specific recommendations of the Transition Policy advice 1.0 serving as the guiding framework for the discussions. Interviewees were asked about 1) the progress of the sub-recommendations; and 2) any recommendations for the (further) implementation of these sub-recommendations. In the second round, twelve interviews were conducted, including one paired interview. For this round, a questionnaire was developed and aligned with Radboud University (Rebecca van Eijden and Professor Ingrid Visseren-Hamakers) to incorporate the perspective of transformative governance. This questionnaire served as a guide and included general questions on the Transition Policy advice 1.0, on developments in the field and drivers or barriers in the transition (Textbox C1). Reports were prepared for all interviews and were shared with the interviewees to check for factual accuracy.

Qualitative analyses of the interview reports

Given the subjective nature of the topic, the need to answer the research question from the perspective of stakeholders, and the exploratory nature of this evaluation, a qualitative analysis of the interview reports was chosen. The analysis of the interview reports was conducted in two ways and independently by two parties; the NCad bureau and Radboud University Nijmegen (Rebecca van Eijden and Professor Ingrid Visseren-Hamakers).

Inductive analysis

The NCad office analysed the interviews inductively, meaning the analysis was performed without a pre-established hypothesis or framework (theory-forming). The first step of the analysis involved a coding round in which the interview reports were divided into text fragments and coded with the corresponding topic, for instance 'validation' or 'innovation'. During a second step, the overarching themes and sub-themes from the codes were identified and assigned to the text fragments. An overview of the identified themes can be found in Table C1. The findings based on the (sub-) themes emerged from the interview reports were then summarised for further processing of the results.

Deductive analysis based on the principles of transformative governance

The Radboud University conducted a primarily deductive analysis, i.e. according to pre-established codes (theory-testing). If a relevant text fragment did not fit under a pre-established code, a new code was added inductively. The codes that were used for the deductive analysis were derived from the principles of transformative governance: ***underlying causes*** and ***forms of governance.*** The IPBES-IPCC definition of 'underlying cause' was used for this: 'Indirect drivers are the forces that underlie and shape the extent, severity and combination of anthropogenic direct drivers that operate in a given place. They include key institutional and governance structures in addition to social, economic and cultural contexts.'[14]

Underlying causes may be regime factors as well as landscape factors. For regime factors, the analysis was guided by the multi-level perspective (MLP) model, which includes market and user preferences, industry, policy, technology, culture and science. A decision was taken to combine science and technology because these factors often coincide in this transition. At a *landscape level*, the analysis was conducted in terms of financial and cultural aspects (values). For the governance forms, the five governance approaches of transformative governance mentioned earlier were applied.

Evaluation of the progress of the transition progress

A reflective evaluation approach, extending beyond specific advice, was chosen, with the identified themes from the analysis of the interview reports serving as the guiding framework. One observation is that there is an under-representation of socio-cultural (research) field, and an over-representation of current regime players (the established order) among the interviewees. This observation was taken into consideration in the evaluation when interpreting the findings of the analysis. The results produced by the inductive analysis of the interview reports reflect the interviewees' perspective. In addition, the results of the deductive analysis based on the principles of transformative governance, shed light on factors that were not discussed in the interviews. For the evaluations, the results of both analyses were combined. The NCad also conducted an additional analysis of the developments in the Netherlands based on desk research.

[14] Pörtner, H.O. et al. (2021). Scientific outcome of the IPBES-IPCC co-sponsored workshop on biodiversity and climate change. IPBES secretariat, Bonn, Germany, https://doi.org/10.5281/zenodo.4659158.

Tabel C1. *Thematic codes defined from the interview reports*

Themes	Codes	Description
Regulatory research	Regulatory_3R	3R issues and initiatives concerning regulatory research, other than only replacement
	Regulatory_acceptance	Acceptance of animal-free innovations within regulatory research
	Regulatory_innovation	Innovative methodologies and their development that are or could be applied within the regulatory frameworks
	Regulatory_regime	The (current) regulations, guidelines, practices, and stakeholders involved in regulatory research
	Regulatory_transition	Fragments concerning the transition from regulatory research to animal-free research; opportunities to change the process
	Regulatory_validation	Validation and acceptance of animal-free innovations within the regulatory frameworks
Fundamental research	Fundamental_3R	3R issues and initiatives concerning fundamental research, other than only replacement
	Fundamental_innovation	Acceptance of animal-free innovations within fundamental research
	Fundamental_public private	Collaborations between academia – industry
	Fundamental_regime	The (current) modus operandi, research questions, practices and the stakeholders involved in fundamental research
	Fundamental_transition	Fragments concerning the transition from fundamental research to animal-free research; opportunities to change the regime
	Fundamental_validation	Validation and acceptance of animal-free innovations within the fundamental science
Translational research	Translation_human research	Human research or research using models that are relevant to humans, which have a better translational value than animal-based research
	Translation_international	International developments in translational research
	Translation_multidisciplinary	Collaborations between fields of expertise in translational research
	Translation_regime	How is translational research regarded, how is it used and based on what scope
	Translation_transition	Transition from translational research to animal-free research
Cross-domain	Education	Education of students to cultivate a new generation with a different mindset. Education of professionals to allow more space for non-animal innovations in current project proposals and evaluations

Themes	Codes	Description
	Ethical issues	Ethical considerations for the transition, for instance dealing with sickness, risk acceptance
	Human research	Research involving humans or using more human-relevant models
	International collaboration	Collaboration from a policy perspective with other countries. Regulatory and fundamental research
	Multidisciplinary	Collaboration between fields of expertise, between stakeholders, and between animal-free and animal-based research
	National_regime	What does the regime look like in the Netherlands? Who are the stakeholders? What are the practices and assumptions? What are the rules?
	Public_private collaboration	The collaboration between fundamental research and industry, likely involving regulatory research
	Target scenario	Processes, reactions, findings of target scenarios
	Target	Regarding a target in general, where the categorization below does not apply
	Target_year	Regarding the effects of and opinions on mentioning a specific year
	Target_ambition	Regarding ambition and realism, and their consequences
	Target_number	Regarding the number of laboratory animals used as the target
	Transition	General comments on the transition
	Transition_funding	National initiatives for funding animal-free innovations
	Transition_innovation	(Development of) innovative methods; unclear framework for application
	Transition_international	International developments in the transition that are relevant or are linked to the transition in the Netherlands
	Transition_multidisciplinary	Processes for collaboration between fields of expertise, between stakeholders, animal-free and animal based research
	Transition_open data	Open data, open science, systemic reviews and the importance of the transition
	Transition_Policy Advice 1.0	General comments on the transition Policy Advice 1.0: how it has been received and what impact it has had

Text Box C1 Questionnaire for the second round of interviews

General questions

1. **Are you familiar with the Transition Policy Advice that the NCad published in 2016?**
   a. What do you think of this Policy Advice?
   b. To what extent would you say the recommendations have been implemented?
   c. What do you see as the main barriers to implementation or low implementation of the advice? With which stakeholders, with which applications, and so on? (Keep all aspects of the MLP in mind).
   d. What can be done to address these key bottlenecks?
2. **What do you think of the transition to animal-free innovation?**
   a. Do you believe this transition is important? Why?
   b. Are there more general trends and norms in society that hinder or promote the transition? For instance, economic thinking, standards on innovation, standards on health and safety, lack of knowledge of the uncertainties of animal testing, human-animal relations.
   c. How do you view the options of solutions other than the deployment of non-animal innovations to reduce the use of laboratory animals? For instance, dealing with disease, preventing disease, dealing with/accepting risk, stopping activities that require animal testing but that do not contribute to health/safety (for instance in animal husbandry)/preventing certain substances from entering the market.
3. **Have steps been taken at your institute/company/discipline to phase out animal testing since the Transition Policy Advice 1.0?**
   a. Where do you see the biggest barriers? Where do opportunities lie?
   b. Which stakeholders influence these barriers and opportunities? In what ways?
   c. Is there sufficient multidisciplinary collaboration for this issue? If so, how does your discipline contribute to this? If not, what can be improved?
   d. Do you think the government (national and/or EU) should aim for animal-free models? If so, how?
4. **Who do you think needs to take steps towards the acceleration of a transition towards the use of animal-free innovations?**
   a. What needs to change amongst the actors mentioned?

Additional questions for contract research organisations/industry

1. **How is the decision to conduct an animal experiment critically assessed?**
   a. Is there a strategy at your company for prioritising or developing non-animal methods?
   b. Do you think that the opportunity for animal-free research is taken into account sufficiently every time when making these considerations? What are the main drivers for this?
   c. What can be improved in the process of valorisation and acceptance of animal-free methods?
   d. How are laws and regulations affecting the industry's transition?
   e. How are more general, social trends and norms influencing industry transitions?
2. **Do you see benefits in moving away from animal models? What do you think the advantages or disadvantages are?**
3. **How can industry in general contribute to the transition to animal-free research?**

Additional questions for academia

1. **How is the decision to conduct an animal experiment weighed up critically?**
   a. Is there a strategy in your discipline/institution for prioritising or developing non-animal methods?
   b. Do you think that the opportunity for animal-free research is taken into account sufficiently every time when making these considerations? What are the main drivers for this?
   c. What advantages or disadvantages is experienced in academia when opting for an animal-free model? What are the advantages or disadvantages for individual researchers?
   d. How do you view the role of a target scenario when deciding on a model?

2. **How do you view the role of academia in the transition to animal-free research?**
   a. Can the academy fully fulfil this role at this point in time? If not, why not?
   b. What can be improved in the process of valorisation and acceptance of animal-free methods?
3. **Do you see a shift in research practice towards non-animal innovations?**
   a. If not, why not?
   b. If so, do you have examples/proof of this? Do you see that reflected in your facility for laboratory animals?
4. **As a research institute, do you want to make an effort to reduce the use of laboratory animals? In this respect, do you feel a responsibility to do so or not?**
   a. Is this aspect taken into account in training? If so, in your opinion, is this already sufficient? If not, why not and do you think this should change? How? What are the bottlenecks/opportunities for this change?

Additional questions for patients/consumer associations

1. **Is it important to you that animals in scientific research are not used? Is that also a topic discussed with your members or that you get asked about?**
2. **Do you think it is important for patients and/or consumers to know how medicinal products were created/marketed and whether or not animals were used in the process?**
3. **Do you think patients/consumers are aware of the use of animal testing?**
4. **Does your association want to promote 'animal-friendly' methods, means or products?**
   a. If so, how? And if not, why not?
   b. What barriers do you see when it concerns moving away from animal testing?
5. **Do patients/consumers feel they are being listened to? Who is listening/not listening to them?**
6. **It is generally believed that people's main value is having a sense of safety and society's assessment of risk (risk perception). What is this assumption based on? Has this been explored?**
   a. Do people have adequate access to reliable information to understand the number of animal tests done for marketing medicinal products or chemicals?
   b. What role does knowledge play in the values that are a factor in this? Is it true that there is a perception that animal testing guarantees safety? Where does that idea come from?
   c. Is there a visible change in the values that people feel are important?

Additional questions for animal rights associations

1. **The interests of animals are not properly safeguarded. Killing animals, for instance, is not seen as problematic from an animal welfare perspective if it is done in a certain way. But killing animals is problematic from an animal rights or intrinsic value point of view, or based on the notion of the integrity of the animal. From what perspective are the interests of laboratory animals generally safeguarded?**
   a. Why is the welfare perspective the only one assumed?
   b. How could this be improved? Which actors need to start taking steps for this to happen?
2. **Where do you see resistance to the transition to animal-free research?**
   a. Where do you see the biggest barriers? Where do opportunities lie?
   b. What are the opposing forces and how can their voices gain more strength?
3. **It is generally believed that people's main value is having a sense of safety and society's assessment of risk (risk perception). What is this assumption based on? Has this been explored?**
   a. Do people have adequate access to reliable information to understand the number of animal tests done for marketing medicinal products or chemicals?
   b. What role does knowledge play in the values that are a factor in this? Is it true that there is a perception that animal testing guarantees safety? Where does that idea come from?
   c. Is there a visible change in the values that people feel are important?

Additional questions for regulators/legislation

1. **How is the decision to conduct an animal experiment weighed up critically?**
   a. Does your institute have a strategy for prioritising or developing non-animal methods?

b. Do you think that the opportunity for animal-free research is taken into account sufficiently every time when making these considerations? What are the main drivers for this?
c. Do you think regulators should do more to encourage the use of animal-free methods and discourage the use of laboratory animals? Is there enough knowledge amongst regulators about animal testing methods?
d. What can be improved in the process of valorisation and acceptance of animal-free methods?
e. How does the international legal framework align with our ambition to reduce animal testing? What will it take to get this framework to start taking steps? Japan, FDA, etc.

2. **Do you see benefits in moving away from animal models? What do you think the advantages or disadvantages are?**
   a. Do regulators have everything they need to assess non-animal data for the authorisation of a medicine or the assessment of a chemical substance? If so, do you see opportunities for improvement? If not, what is required for this?
3. **The general assumption is that people perceive safety and risk perception as having the most value. What is this assumption based on? Has this been explored?**
   a. Do people have adequate access to reliable information to understand the number of animal tests done for marketing medicinal products or chemicals?
   b. What role does knowledge play in the values that are a factor in this? Is it true that there is a perception that animal testing guarantees safety? Where does that idea come from?
   c. Is there a visible change in the values that people feel are important?

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