

Research Involving Non-Human Primates: Four Policy Scenarios for the Netherlands

**Report by The Committee on
Research Involving Non-Human Primates**

**Commissioned by the Minister of Education, Culture and
Science (OCW)**

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Summary

In November 2022, the Dutch House of Representatives requested that the government investigate if the number of experiments conducted on non-human primates (NHPs) could be reduced. In response, the Minister of Education, Culture and Science (OCW) established this committee in December 2023. The committee was tasked with examining the possibility to further reduce the number of experiments involving NHPs without compromising research that is strictly necessary for controlling life-threatening diseases and outbreaks of infectious diseases affecting public health.

The committee was not asked to provide policy advice but to conduct "an examination of what is possible and what is not." Therefore, this report consists of two parts. In the first part, the committee presents the results of its investigation into ways to reduce NHP experiments. The second part outlines four policy scenarios, which result from different weightings of relevant arguments. The committee does not express a preference for any of the policy scenarios. However, on certain issues, the committee does formulate clear conclusions that apply to all policy scenarios.

The committee's findings are based on two primary sources of information: literature review and interviews with experts. The committee's own expertise played a crucial role in interpreting the literature and expert discussions. The committee made working visits to the two Dutch NHP research facilities and held two consultations—one with researchers specializing in New Approach Methodologies (NAMs) and another with representatives of societal interest groups. Finally, bioinformatician Dr. James Gallant was commissioned to analyse international literature on NHP research, providing insights into key characteristics of global NHP research.

Ethics

The discussion on the necessity of animal research in general—and NHP research in particular—as well as discussions on the reduction of such experiments, extends beyond scientific facts. It also involves a moral dimension: what do we consider valuable, good, and important? This falls within the domain of ethics. Any position in the debate on using NHPs as test subjects is informed by perspectives on and judgments about:

- the intrinsic value of animals,
- the value of human objectives,
- the weighting of these different values in relation to each other.

This ethical context is crucial when making decisions about the future of NHP research.

Animals have value for humans, which is often the reason they are used in research: they can provide crucial information for scientific knowledge and human health. However, animals also have intrinsic value, meaning their worth exists independently of their utility or function. The attribution of intrinsic value is often linked to an animal's ability to suffer.

NHPs occupy a special position—ethically, legally, and scientifically. They also hold a distinct place in societal debate due to their emotional and symbolic significance. NHPs exhibit cognitive and social traits like humans, value autonomy, and engage in future-oriented behaviour. Consequently, they are often accorded a different status in public discourse compared to other experimental animals.

In the context of animal experiments, both the intrinsic value of animals and the purpose of scientific research must be weighed in a harm-benefit analysis. The committee's report discusses various

ethical frameworks for evaluating these trade-offs, including the utilitarian ethical framework, the deontological ethical framework, and the relational or care ethics framework. The choice of a particular ethical framework is not purely scientific; political and societal factors must be considered too. The harm-benefit analysis, which is central to European and Dutch regulations on animal experiments, is primarily grounded in a utilitarian ethical framework.

In addition to the harm-benefit analysis, ethical evaluation of animal experiments in the Netherlands is guided by the Three Rs (3Rs):

- *Replacement* of animal experiments with alternative methods such as computational models, cell cultures, and other in vitro techniques. Animal experiments are permitted only when no reasonable alternatives exist.
- *Reduction* in the number of animals used in experiments through advanced statistical methods and study designs, ensuring that the number of test animals is minimized while maintaining sufficient statistical power.
- *Refinement* of experimental procedures to improve the welfare of animals and minimize distress through better living conditions and optimized experimental design.

However, the 3R approach has limitations. It is applied on a case-by-case basis and therefore has limited impact on the structural reduction of animal experiments in science. Greater progress is expected from a vision-based approach in the transition to animal-free research. Such an approach sets long-term objectives for animal-free research within a specific scientific domain, providing a roadmap for answering key research questions with minimal animal experimentation—this is referred to as the ‘roadmap approach to animal-free research’, or ‘roadmap approach’ for short.

Legislation and Regulation

Animal experiments in the European Union are regulated by Directive 2010/63/EU on the protection of animals used for scientific purposes (Animal Experimentation Directive). This directive sets strict requirements for the ethical review and justification of animal experiments, animal care, and the promotion of alternative methods to reduce the use of animals in experiments. The aim is to ensure animal welfare while enabling scientific progress. Several articles within the directive specifically address NHPs.

The Netherlands implemented the European Animal Experimentation Directive in 2014 by revising the Dutch Animal Experiments Act (Wod). The directive and the Wod follow a ‘no, unless’ principle: this means animal experiments are not allowed unless:

- there are compelling reasons to conduct the experiment,
- no suitable alternative methods exist,
- the examination is conducted by licensed institutions,
- the examination is performed by qualified personnel.

Additional requirements apply to NHP research. Experiments on NHPs may only be conducted in essential biomedical fields that benefit humans and only if no alternative methods are available. The Wod sets broader conditions for NHP research than the commission’s mandate, which is limited to ‘infectious diseases that threaten public health’ and ‘life-threatening diseases’ as criteria for allowing NHP experiments.

The committee explores, in line with its mandate, the possibilities of applying the criteria of ‘infectious diseases that threaten public health’ and ‘life-threatening diseases,’ even though these are stricter than the criterion of the Wod. Examining these stricter criteria for the admission of NHPs is

meaningful, as they could be implemented without violating the Wod or the underlying EU Directive on Animal Experiments—by imposing conditions on the funding of the Biomedical Primate Research Center (BPRC).

In the Netherlands, several authorities and advisory bodies are responsible for implementing animal experimentation policy:

- NVWA (Netherlands Food and Consumer Product Safety Authority) acts as the regulatory body, granting institutional licences for animal experiments and ensuring compliance with regulations.
- IvDs (Animal Welfare Authorities) oversee the internal execution of animal experiments within institutions, with a specific focus on animal welfare and adherence to the 3Rs.
- CCD (Central Committee on Animal Experiments) is the overarching authority responsible for licensing animal experiments in the Netherlands.
- DECAs (Animal Experimentation Committees) are often, but not necessarily, affiliated with research institutions and advise the CCD on licence applications.
- NCad (Netherlands National Committee for protection of animals used for scientific purposes) offers solicited and unsolicited advice to the Minister of Agriculture, Fisheries, Food Security and Nature (LNVN), the CCD, and IvDs regarding the acquisition, breeding, housing, care, and use of animals in experiments.

Dutch NHP Facilities

Currently, NHP experiments are conducted at two research facilities in the Netherlands: the BPRC in Rijswijk and the Netherlands Institute for Neuroscience (NIN) in Amsterdam.

The housing of NHPs at the BPRC meets European standards. Additionally, the BPRC adheres to the more advanced guidelines of the UK 3R Centre. A key requirement for the breeding colony at the BPRC is that it must maintain a minimum size. The current BPRC colony is already relatively small, with approximately 1,000 monkeys living in different groups. However, it remains large enough to sustain an outbred population, ensuring sufficient genetic diversity among the NHPs. This genetic diversity is crucial for preventing inbreeding, which could threaten animal health and undermine the validity of the research model.

The second research facility conducting NHP experiments is the NIN. Brain research with NHPs at the NIN focuses on the visual system. The NIN is part of the Royal Netherlands Academy of Arts and Sciences (KNAW) and has a dedicated primate unit with 16–20 rhesus macaques. These NHPs are used for fundamental research on visual perception, attention, and consciousness. Since 2009, the KNAW has been discussing whether it should continue to maintain its own NHP facility.

Applications of NHP Research

NHPs play an important role in drug development and regulation—not in terms of numbers, but because they are still considered indispensable at certain critical stages of the drug development process. However, there is no general agreement among scientific researchers regarding this indispensability.

NHP experiments are particularly important in preclinical research on the efficacy and safety of drugs. In the Netherlands, such experiments are conducted at the BPRC, though Dutch companies also make use of NHP facilities abroad. Additionally, NHPs still play a role in legally required regulatory safety testing of drugs and medical materials—although this type of research is not conducted in the Netherlands.

The Medicines Evaluation Board (CBG) encourages research into the necessity and justification of NHP use. In collaboration with academic researchers, regulatory authorities in Europe, and industry, questions are being addressed regarding the translational value of NHPs and the level of evidence required to enhance drug safety. There is also ongoing reflection on the criteria that NAMs must meet to gain international acceptance. Based on discussions with experts, the committee concludes that regulatory authorities overseeing clinical research, such as the European Medicines Agency (EMA) in Europe and the Central Committee on Research Involving Human Subjects (CCMO) in the Netherlands, are adopting an increasingly critical stance on the use of NHPs.

The committee discusses the three types of NHP research applications mentioned in its mandate: infectious diseases that threaten public health, life-threatening diseases, and other scientific research.

Key characteristics of an infectious disease that threatens public health include:

- *High transmissibility*: The disease can be easily transmitted between humans, between animals, and between animals and humans, enabling rapid spread.
- *Potential for severe consequences*: The disease can cause serious health complications, including hospitalisation, long-term damage to the body, or death.
- *Limited or no immunity in the population*: People have little or no immunity against the pathogen, which can contribute to the rapid spread of infection.
- *Societal disruption*: The disease can disrupt normal societal functions, including healthcare systems, economies, and daily life. This disruption does not necessarily have a natural cause; an infectious disease could also be intentionally used by a hostile actor to cause such effects.

Some argue that NHPs play a crucial role in infectious disease research because of all animals, their immune system is most similar to that of humans, making them the most suitable model for vaccine and drug testing. NHP research is conducted during the preclinical phase of vaccine development, where candidate vaccines are often tested for safety and efficacy before proceeding to human trials.

Part of the committee's mandate is to "examine strategic European autonomy and the (reduction of) dependence on other countries, for example in the context of vaccine development." The issue of strategic autonomy in NHP research is particularly relevant for pandemic infectious disease control and vaccine development. While Dutch researchers played a key role in identifying the coronavirus and developing vaccines, they did so within large international collaborations. However, their contributions were only possible due to their own research experience, Dutch research facilities, and the researchers' strong international reputation. According to virologists consulted by the committee, NHPs remain crucial for research on emerging infectious diseases that threaten public health. A Dutch NHP facility thus contributes to strategic autonomy in the event of a future pandemic. This does not mean that phasing out NHP research is impossible, but the committee identifies increased dependence on foreign facilities as a risk. When assessing this risk, policymakers must also consider the current erratic developments in geopolitical relations, particularly developments in Europe's relations with the United States and China.

The term 'life-threatening disease' is primarily used in political discourse. However, in scientific and clinical practice, it lacks a precise definition. After a detailed analysis, the committee concludes that 'life-threatening' as a disease classification cannot be scientifically substantiated sufficiently to serve as a criterion for permitting NHP research. Consequently, the committee refers to 'life-threatening and other serious diseases' in the remainder of its study. This implies that applying this criterion will

require a political decision regarding where to draw the line between more and less severe diseases—and which diseases thus justify the use of NHP research.

Other scientific research involving NHPs primarily consists of fundamental research, though it partially overlaps with the previous category of research into life-threatening and other serious diseases. Examples include various neuroscientific studies, such as research on Parkinson's disease, as well as studies on cancer, genetic disorders, cardiovascular diseases, and diabetes.

An analysis of international literature indicates that the Netherlands is a significant contributor to NHP research. The country ranks eighth globally in terms of the number of published studies involving NHPs. Within the EU, the Netherlands is a key player—contributing to 63% of all published NHP research in the EU in 2021.

Translatability of NHP Models

Several sources indicate that NHP research remains a significant research model for studying both infectious diseases and life-threatening or otherwise serious human diseases. NHP research is still widely applied where the complexity of human biology and disease processes are difficult to replicate in other models, and where ethical and practical considerations directly limit human studies. In testing the safety and efficacy of new drugs and treatments, NHPs are often considered necessary to predict how humans will respond to these drugs or treatments. Opponents of NHP research focus much of their critique on this argument, reasoning that there is increasing evidence that the translatability of NHP models to humans falls short.

Some experts consulted by the committee suggest that further research is needed into the translatability of NHP models to humans. When are NHP experiments necessary to safely demonstrate the effect on humans? When do experiments on small animals or alternatives to animal experiments suffice? And do these alternatives provide sufficient insight into the effects on humans? Others argue that there are diseases for which NHPs still represent the best model—particularly when systemic effects across various organ systems are involved. Moreover, the translatability of even the best available animal models (including human models) is never perfect, which leads to questions about the necessity of animal models in general, as well as the translatability of other models—important discussions that fall outside the scope of the committee's mandate.

NAMs

NAMs include research using human tissues, stem cells, cell culture systems, computational models, and data analyses. NAMs are not only developed to replace animal experiments, but they also contribute independently to understanding human disease mechanisms and the effects of chemicals on human cells and tissues.

Key groups of NAMs include:

- *Organ-on-a-chip*: miniature models of human organs that can simulate certain physiological processes;
- *Organoids and cell culture models*: 3D cell structures or 2D cell cultures that model human tissues;
- *Computational models and artificial intelligence*: advanced simulations of biological processes and big-data analyses of large datasets.

Strictly speaking, Controlled Human Infection Models (CHIMs) and systematic literature reviews are not considered NAMs, but since both can significantly reduce NHP testing, they are nonetheless discussed by the committee in the chapter on NAMs.

There are various ways in which NAMs could serve as an alternative to NHP experiments. One advantage of NAMs is that they can provide insights into the effects and risks of a treatment, allowing more confident application of that treatment directly to humans without first conducting experiments on NHPs. Second, NAMs can, in some cases, offer better insights into the effects and risks of treatments than experiments with NHPs. Third, NAMs can help refine the choice between different animal models when an animal experiment is still necessary. Lastly, because NAMs often involve single-organ models, they can provide more precise information about the treatment, allowing the researcher to refine the research question or improve the treatment before proceeding with experiments on NHPs or humans. This can lower the burden on NHPs or reduce the number of NHPs needed—or eliminate the need for NHPs entirely.

Since an animal experiment and a NAM never measure the same variables, animal experiments cannot simply be replaced on a one-to-one basis by NAMs. The research question must guide this process, and often a combination of NAMs serves as the alternative. This research question should be the starting point in the development and implementation process of NAMs, with the anticipated 'context of use' playing a critical role.

The diversity of NAMs and the broad range of research questions and contexts of use make it difficult to directly compare the use of NAMs with NHP experiments. However, researchers observe promising NAMs that, in the short or long term, could partially replace NHP experiments (see [Table 4](#) in the report). NHP experiments, in comparison to many NAMs, have significant limitations in their qualification for human-relevant contexts of use. Currently, however, NAMs are not yet capable of answering all research questions for which NHP experiments are considered necessary.

Regulatory authorities also focus heavily on the reduction and replacement of animal experiments in general, and NHP experiments in particular. An additional reason for this is the global shortage of NHPs during the SARS-CoV-2 crisis. EMA and CBG encourage NAM researchers to establish contact with regulatory authorities at the earliest possible stage, so that the entire NAM development and implementation process begins with a clear problem statement, 'fit for purpose,' and 'context of use,' thereby increasing the likelihood of acceptance by EMA and CBG.

Four Policy Scenarios

The report is in two parts. In Part 1, the committee reports the results of its investigation into what is possible and what is not regarding the reduction of NHP experiments. In Part 2, the committee presents four policy scenarios. In this way, the committee fulfils its mandate to investigate what is possible and what is not, without providing a policy recommendation (see [Table 5](#) for an overview).

In Part 1, the committee addresses several sub-questions. These concern in particular: the historical and societal background of NHP experiments, possible ethical-philosophical frameworks, relevant national and international laws and regulations, Dutch NHP facilities, the number of NHP experiments in the Netherlands, and various aspects of international NHP research.

However, on the answer to some other key sub-questions, there is no scientific consensus. This concerns particularly: the translatability of NHP experiments, the importance of NHP experiments for various fields of science, the prospects in the development of NAMs, and the question of which

ethical framework is most adequate. In these cases, the committee presents the most complete possible picture of the different and often contradictory answers to such sub-questions.

On topics where there is no scientific consensus, the committee cannot describe the situation in an unequivocal way. For these topics, political and policy choices are necessary, taking the scientific analysis into account, but with the understanding that this analysis does not offer a decisive basis for the choice. Therefore, the committee develops four policy scenarios in Part 2 of the report for possible future developments regarding the use of NHPs. Adhering to the mandate of not providing policy advice, the committee presents these policy scenarios in the most balanced and neutral manner possible—it has no preference of its own.

The policy scenarios also have much in common. The committee therefore formulates several conclusions that apply to all policy scenarios. These relate to:

- The role of DEC's and CCD and their reflection on the harm-benefit analysis
- The importance of NAM research
- The proactive role of regulatory authorities such as EMA and CBG
- The importance of the roadmap approach: for NHP research, the roadmaps of brain research, immunology, and infectious disease research are particularly relevant
- The importance of European coordination and collaboration in NAM and NHP research
- The importance of systematic literature reviews
- Transparency in government communication regarding policy choices made
- The necessity for all NHP research to be published according to the ARRIVE guidelines

Policy Scenario 1: Phasing Out NHP Research in the Netherlands

In policy scenario 1, the Dutch government decides to stop funding the BPRC. Existing research on NHPs will be phased out, and public funding for the BPRC as a research facility and for NHP research will cease. Sufficient funding will still be necessary to ensure the proper housing of the NHPs during their 'retirement' until the last passes away.

An important consideration in this decision is that some believe that research with NAMs and direct human research offer sufficient prospects for high scientific quality without NHPs, as NHP models are less translatable to humans than often assumed. However, not everyone agrees with this. Many researchers, including NAM researchers, still see the NHP model as a necessary element in research on infectious diseases and life-threatening and otherwise severe diseases. In their view, an implication of this policy scenario is that research on infectious diseases and life-threatening and otherwise severe diseases in the Netherlands would lose quality.

This scenario can be defended within two different ethical frameworks. The first is a deontological framework, where humans are considered equal to NHPs and thus the use of NHPs for the benefit of humans is not acceptable. But it can also be defended within a utilitarian ethical framework if the benefits of NHP experiments do not outweigh the harm to the NHPs.

In this policy scenario, it is still possible for organizations (companies, universities, and even the BPRC without government funding) in the Netherlands to conduct NHP research, provided it is approved by the CCD.

Summary of Benefits, Losses, and Risks

The *benefit* of this policy scenario is that NHP research in the Netherlands will be phased out. (Caveat: this phase-out primarily applies to NHP research at the BPRC, as programs at other institutes such as the NIN and pharmaceutical companies cannot be directly controlled by the Dutch government.) The *loss* that the Netherlands must accept in this policy scenario is that it becomes completely dependent on foreign NHP research. As a result, the Netherlands will be in the ethically difficult position of not

conducting its own NHP research but still benefiting from medical innovations, such as vaccines and medicines, that were developed using NHPs abroad. A second *loss* is the increased dependency on foreign NHP research, making it more difficult for the Netherlands to respond to a new pandemic. The first *risk* is that the Netherlands will no longer be able to monitor the quality of NHP facilities. A second *risk* is that good research lines using NHPs abroad will continue, causing the Netherlands to lose knowledge and experience.

Policy Scenario 2: Reduction of NHP Research in the Netherlands

In policy scenario 2, the Netherlands decides to reduce NHP research but not completely phase it out. The consideration here is that for research on infectious diseases and some life-threatening and otherwise severe diseases, the use of NHPs is still necessary.

This policy choice is based on the belief that NAMs are not yet sufficiently available or qualified and that NHP models are sufficiently translatable to humans, making them an important element in research aimed at controlling infectious diseases that threaten public health and for research on some life-threatening and otherwise severe diseases. Not everyone shares this belief, however: some argue that the translatability of some NHP research is insufficiently clear.

Ethically, this policy scenario rests on the view that humans are morally superior to animals and that animals may be used for the benefit of humans when significant human interests are at stake.

This policy scenario can be realised via two different sub-scenarios, depending on the conditions attached to the government funding of the BPRC. The sub-scenarios differ in how the reduction is implemented. In sub-scenario 2a, research is only allowed on infectious diseases that threaten public health. In sub-scenario 2b, research is also allowed on a select number of specified life-threatening and otherwise severe diseases. This means that a policy choice must be made about where the 'cut-off' point lies between severe and not-so-severe diseases and thus between permitted and non-permitted NHP experiments.

Summary of Benefits, Losses, and Risks

The first *benefit* of this policy scenario is that NHP research in the Netherlands is substantially reduced (with the same caveat regarding the NIN and industry as in the first policy scenario). The second benefit is that the Netherlands maintains its own facility and capacity to contribute to vaccine development, thereby preserving its pandemic resilience. The BPRC retains a colony of NHPs and continues research on infectious diseases that threaten public health to maintain its facilities and expertise for pandemic vaccine development. The *loss* that the Netherlands accepts in this policy scenario is that some other NHP research lines will be phased out, depending on the choices within the sub-scenarios. The Netherlands will thus find itself in the ethically challenging position of not conducting certain NHP research itself but still benefiting from medical innovations, such as vaccines and medicines, that were developed using NHPs abroad. Furthermore, this creates a *risk* that good researchers may leave for other countries, leading to a loss of knowledge and experience. A second *risk* of fewer NHPs is that certain studies may no longer be feasible, either due to the limited availability of NHPs or insufficient statistical power.

Policy Scenario 3: Maintaining NHP Research in the Netherlands

In policy scenario 3, the Netherlands decides to maintain the current research with NHPs. The main consideration is that societal harm will be prevented by continuing research on infectious diseases that threaten public health, on treatments for life-threatening and otherwise severe diseases, and potentially on brain disorders (also depending on KNAW policy).

In this policy scenario, emphasis is still placed on the legally required 3Rs approach: replacement, reduction, and refinement of NHP experiments. The focus is on further improving

animal welfare and conducting systematic literature reviews to provide better scientific justification for the use of NHPs.

NHP research is still considered essential for certain scientific issues, especially in the fields of infectious diseases, immunology, and neuroscience. It is, however, possible that the criteria in the harm-benefit analysis by DEC and CCD could be adjusted.

Summary of Benefits, Losses, and Risks

The *benefit* of this policy scenario is that current research on infectious diseases that threaten public health and on life-threatening and otherwise severe diseases can continue. The *loss* that the Netherlands accepts in this policy scenario is that there is no reduction in NHP research. This means that this policy scenario carries the *risk* of insufficient consideration of societal discontent with the continued existence of NHP research.

Policy Scenario 4: Possible Increase in NHP Research in the Netherlands

In policy scenario 4, an increase in the number of NHPs and NHP experiments in the Netherlands may be allowed if NAMs are insufficient to answer the research questions. A key consideration is that the use of NHPs could play an important role in controlling infectious diseases that threaten public health, in the treatment of life-threatening and otherwise severe diseases, and in fundamental research. Criticism of the translatability of NHP experiments is acknowledged, but systematic literature reviews will be used to prevent experiments that, based on the results of previous studies, have little chance of success or are redundant. In this policy scenario, it is also possible that the number of NHP experiments will not increase if sufficient NAMs become available, or if a decision is made at the European level to establish a central facility in another country.

A crucial part of this scenario is that the Netherlands advocates at the European level for centralising all NHP research in one primate centre. The BPRC could be a candidate for this, as it currently plays a prominent and high-quality role in the breeding, housing, and research of NHPs. This would lead to an increase in the number of housed NHPs in the Netherlands but should result in a reduction of overall NHP use in Europe. Thus, the Netherlands would take on the ethical burden of housing NHPs for other European countries. A scenario where all NHPs in Europe are centralised, like strategies that have been successful in research centres for space exploration and elementary particle physics, also implies that such a centre could be located in a country other than the Netherlands.

Summary of Benefits, Losses, and Risks

The *benefit* of this policy scenario is that in addition to current research on infectious diseases that threaten public health and on life-threatening and otherwise severe diseases, other NHP research becomes possible. The necessary increase in the number of NHP experiments is allowed in this policy scenario, but it is not mandatory—it is also possible that, with NAMs developed soon, the research questions can be answered without increasing the number of NHPs used. The *loss* that the Netherlands accepts in this policy scenario is that no reduction in NHP research occurs on Dutch ground, even though there may be ethically valid reasons for such a reduction. This carries the risk that insufficient attention is given to societal discontent with the existence of NHP research.

Samenvatting

De Tweede Kamer heeft in november 2022 de regering verzocht onderzoek te doen naar de mogelijkheid om het aantal proeven op niet-humane primaten (NHP's) te verlagen. De minister van Onderwijs, Cultuur en Wetenschap (OCW) heeft daarop in december 2023 deze commissie ingesteld. De commissie kreeg als taak onderzoek te doen naar de mogelijkheid om het aantal proeven met NHP's verder te verlagen zonder dat dit gevolgen heeft voor het onderzoek dat strikt noodzakelijk is voor de bestrijding van levensbedreigende ziekten en uitbraken van infectieziekten die de volksgezondheid bedreigen.

De commissie is niet gevraagd beleidsadvies te geven, maar om “een onderzoek naar wat kan en niet kan”. Daarom heeft dit rapport twee delen. In het eerste deel beschrijft de commissie de resultaten van haar onderzoek naar mogelijkheden om het aantal NHP-proeven te verminderen en in het tweede deel geeft de commissie vier beleidsscenario's. Deze zijn het resultaat van verschillende wegen van relevante argumenten. De commissie spreekt geen eigen voorkeur voor een van de beleidsscenario's uit. Dat betekent overigens niet dat de bevindingen kleurloos zijn. Op een aantal punten formuleert de commissie duidelijke conclusies die gelden voor alle beleidsscenario's.

De commissie baseert zich op twee soorten bronnen: literatuuronderzoek en interviews met diverse experts. Bij de interpretatie van de literatuur en de gesprekken met deskundigen speelt de eigen expertise van de commissieleden een belangrijke rol. De commissie heeft werkbezoeken gebracht aan de twee Nederlandse NHP-faciliteiten en heeft twee consultaties gehouden—de eerste met onderzoekers van 'New Approach Methodologies' (NAM's) en de tweede met vertegenwoordigers van maatschappelijke belangenorganisaties. Tot slot heeft de commissie door bio-informaticus dr. James Gallant een analyse van de internationale literatuur laten uitvoeren. Deze analyse richt zich op wetenschappelijke publicaties over onderzoeken op NHP's en geeft zicht op belangrijke karakteristieken van het internationale NHP-onderzoek.

Ethiek

De discussie over de noodzaak van onderzoek met behulp van dieren in het algemeen en NHP's in het bijzonder—evenals een discussie over afbouw van dier- en NHP-proeven—vraagt niet alleen om feitelijke wetenschappelijke onderbouwing. Het gaat ook over een morele afweging: wat vinden we waardevol, goed en belangrijk? Dat is het terrein van de ethiek. Elke positie in het debat over het gebruik van NHP's als proefdieren gaat samen met visies op en oordelen over:

- de waarde van dieren,
- de waarde van menselijke doelen,
- de weging van deze verschillende waarden ten opzichte van elkaar.

Bij de onderbouwing van keuzes over de toekomst van NHP-onderzoek is deze ethische context belangrijk.

Dieren zijn voor de mens waardevol. Dat is vaak ook de reden om dieren in te zetten voor onderzoek: ze kunnen een bron zijn van relevante informatie voor wetenschappelijke kennis en humane gezondheid. Maar dieren hebben ook een intrinsieke waarde. Dat betekent dat ze een waarde hebben die los staat van nut of gebruikswaarde. De toekenning van intrinsieke waarde wordt vaak gekoppeld aan het vermogen van dieren om te lijden.

NHP's nemen een bijzondere positie in—in de dierethiek, in de wetgeving en in de wetenschappelijke praktijk. En ook in het maatschappelijk debat: de bijzondere aandacht voor onderzoek op NHP's is begrijpelijk gezien de emotionele en symbolische waarde die veelal aan apen wordt gehecht. NHP's lijken cognitief en sociaal veel op mensen, ze hechten aan autonomie en hebben toekomstgerichte projecten—NHP's krijgen daardoor in het maatschappelijk debat vaak een andere status dan andere proefdieren.

Bij dierproeven is niet alleen de waarde en beschermwaardigheid van dieren ethisch relevant. Wetenschappelijk onderzoek wordt gedaan met een bepaald doel dat als waardevol wordt gezien. Beide waarden—die van het dier en die van het resultaat van wetenschappelijk onderzoek—moeten in een schade-baten analyse tegen elkaar worden afgewogen.

De commissie bespreekt verschillende ethische afwegingkaders: het utilistisch ethisch kader, het deontologisch ethisch kader, en het relationele of zorg-ethische kader. De keuze voor een bepaald ethisch kader is geen louter wetenschappelijke zaak, maar moet ook steunen op politieke en maatschappelijke overwegingen. De schade-baten analyse die een centrale rol speelt in de Europese en Nederlandse wetgeving rondom dierproeven stoelt vooral op het utilistisch ethisch kader.

Naast de genoemde schade-baten weging, staan in de ethische toetsing van proefdieronderzoek de zogenaamde 3V's centraal:

- *Vervanging* van dierproeven door alternatieve methoden, zoals computermodellen, celkweek en andere *in vitro* technieken—alleen als alternatieve modellen niet mogelijk zijn, is proefdieronderzoek toegestaan;
- *Vermindering* van het aantal dieren dat nodig is voor onderzoek door het gebruik van geavanceerde statistische methoden en studieontwerpen—het aantal gebruikte proefdieren dient zoveel mogelijk beperkt te worden mits voldoende statistische power overgehouden wordt;
- *Verfijning* door verbetering van de leefomstandigheden van de dieren en van de opzet van experimenten zoals het minimaliseren van belastende handelingen.

Er zijn ook beperkingen aan de 3V benadering. Het toepassen van de 3V's gebeurt namelijk op een *casus-per-casus* basis en heeft daardoor slechts een beperkte impact op de structurele vermindering van proefdiergebruik in de wetenschap. Meer wordt verwacht van de streefbeeldbenadering in de transitie naar proefdiervrij onderzoek: een streefbeeld voor proefdiervrij onderzoek in een bepaald wetenschapsgebied biedt een toekomstvisie op hoe de leidende vragen voor fundamenteel en translationeel onderzoek kunnen worden beantwoord met zo weinig mogelijk dierproeven.

Wet- en regelgeving

In de Europese Unie worden dierproeven gereguleerd door de "Directive 2010/63/EU on the protection of animals used for scientific purposes" (Dierproevenrichtlijn). Deze richtlijn stelt strenge eisen aan de ethische beoordeling en de rechtvaardiging van dierproeven, de zorg voor de dieren, en de bevordering van alternatieve methoden om het gebruik van dieren te verminderen. Het doel is om het welzijn van de dieren te waarborgen en tegelijkertijd de wetenschappelijke vooruitgang te bevorderen. Er zijn verscheidene artikelen in de richtlijn specifiek gericht op NHP's.

Nederland heeft sinds 2014 de Europese Dierproevenrichtlijn in de nationale wet- en regelgeving geïmplementeerd door middel van een herziening van de Wet op de dierproeven (Wod). De Dierproevenrichtlijn en de Wod hebben een “nee, tenzij” karakter: de Wod stipuleert dat in beginsel geen dierproef mag worden uitgevoerd, *tenzij*:

- er zwaarwegende redenen zijn dit onderzoek te doen, en
- er voor het onderzoek geen geschikte vervangende methoden bestaan, en
- het onderzoek wordt uitgevoerd door vergunde instellingen, en
- het onderzoek wordt uitgevoerd door bevoegd en bekwaam personeel.

Voor NHP's gelden nog aanvullende vereisten. Onderzoek op NHP's mag alleen plaatsvinden op essentiële biomedische gebieden ten bate van de mens, mits daarvoor geen alternatieve methoden beschikbaar zijn. De Wod stelt hiermee ruimere voorwaarden aan de toelaatbaarheid van NHP-onderzoek dan in de opdracht aan de commissie gebeurt, waarin sprake is van 'infectieziekten die de volksgezondheid bedreigen' en 'levensbedreigende ziekten' als criteria om NHP-onderzoek toe te staan.

De commissie verkent, in lijn met haar opdracht, de mogelijkheden om de criteria 'infectieziekten die de volksgezondheid bedreigen' en 'levensbedreigende ziekten' toe te passen, hoewel zij strikter zijn dan het criterium van de Wod. Het is zinvol deze striktere criteria voor de toelating van NHP's te onderzoeken, omdat deze geïmplementeerd zouden kunnen worden zonder in strijd te zijn met de Wod of de daarachterliggende EU Dierproevenrichtlijn—namelijk door voorwaarden te stellen aan de financiering van het Biomedical Primate Research Center (BPRC).

In Nederland zijn verschillende autoriteiten en adviesorganen om het dierproevenbeleid uit te voeren:

- NVWA (Nederlandse Voedsel- en Warenautoriteit) verleent als toezichthouder instellingsvergunningen voor dierproeven en controleert of instellingen volgens de regels werken.
- IvD's (Instanties voor dierenwelzijn) houden intern toezicht op de manier van uitvoeren van dierproeven en letten daarbij specifiek op dierenwelzijn en de navolging van de 3V's binnen de instelling.
- CCD (Centrale Commissie Dierproeven) is de overkoepelende autoriteit die verantwoordelijk is voor het verlenen van vergunningen voor dierproeven in Nederland.
- DEC's (Dierexperimentcommissies) zijn vaak, maar niet noodzakelijk, gelieerd aan onderzoeksinstellingen en geven advies aan de CCD over een vergunningaanvraag.
- NCad (Nationaal Comité advies dierproevenbeleid) geeft gevraagd en ongevraagd advies aan de minister van LNVN, de CCD en IvD's over de aanschaf, fok, huisvesting, verzorging en het gebruik van dieren in experimenten.

Nederlandse NHP-faciliteiten

In Nederland worden op dit moment binnen twee onderzoeksfaciliteiten NHP-experimenten uitgevoerd: in het BPRC in Rijswijk en bij het Nederlands Herseninstituut (NIN) in Amsterdam.

De huisvesting van NHP's in het BPRC voldoet aan de Europese standaarden. Daarenboven volgt het BPRC ook de verdergaande richtlijnen van het Britse 3R Centre. Een belangrijke randvoorwaarde bij de grootte van de fokkolonie van het BPRC is dat deze een minimale omvang dient te behouden. De huidige BPRC-kolonie is al relatief kleinschalig, met rond de 1.000 apen wonend in verschillende

groepen, maar groot genoeg om een *outbred* populatie in stand te houden, wat betekent dat er een genetisch voldoende diverse groep van apen beschikbaar is. Deze genetische diversiteit is essentieel om inteelt te voorkomen; inteelt zou de gezondheid van de dieren in gevaar brengen en de validiteit van het onderzoeksmodel ondermijnen.

De tweede onderzoeksfaciliteit waar NHP-experimenten plaatsvinden is het NIN. Het hersenonderzoek met NHP's in het NIN is gericht op het visuele systeem. Het NIN is onderdeel van de Koninklijke Nederlandse Akademie van Wetenschappen (KNAW) en heeft een speciale primatenuit met 16-20 resusapen. Deze apen worden gebruikt voor fundamenteel onderzoek naar visuele waarneming, aandacht en bewustzijn. Al sinds 2009 wordt binnen de KNAW besproken of nog wel een eigen faciliteit voor NHP's moet worden gehandhaafd.

Toepassingen van NHP-onderzoek

NHP's spelen een belangrijke rol bij het ontwikkelen en reguleren van geneesmiddelen—niet in termen van aantallen, maar omdat ze op een aantal kritische momenten in het ontwikkelingsproces van geneesmiddelen vooralsnog onmisbaar worden geacht. Over deze onmisbaarheid is overigens geen algehele overeenstemming onder wetenschappelijke onderzoekers.

Vooraf in preklinisch onderzoek naar de effectiviteit en veiligheid van geneesmiddelen zijn NHP-experimenten belangrijk. In Nederland worden dergelijke experimenten uitgevoerd door het BPRC, maar bedrijven in Nederland maken ook gebruik van NHP-faciliteiten in het buitenland. Ook bij het uitvoeren van het wettelijk verplichte regulatoire veiligheidsonderzoek naar geneesmiddelen en medische materialen spelen NHP's nog steeds een rol—dit soort onderzoek gebeurt niet in Nederland.

Het College ter Beoordeling van Geneesmiddelen (CBG) stimuleert onderzoek naar nut en noodzaak van het gebruik van NHP's. Samen met academische onderzoekers, collega-registratieautoriteiten in Europa en de industrie worden vragen beantwoord over de translationele waarde van NHP's en welke mate van bewijslast echt bijdraagt aan een grotere veiligheid van geneesmiddelen. Ook wordt gereflecteerd op de vraag aan welke criteria NAM's zouden moeten voldoen om internationaal geaccepteerd te worden. Uit gesprekken met deskundigen concludeert de commissie dat er een steeds kritischer houding ten aanzien van NHP's is bij autoriteiten die klinisch onderzoek reguleren, zoals in Europa bij het Europees Medicijn Agentschap (EMA) en in Nederland bij de Centrale Commissie Mensgebonden Onderzoek (CCMO).

De commissie beprekt de drie soorten toepassingen van NHP-onderzoek die in haar opdracht worden genoemd: infectieziekten die de volksgezondheid bedreigen, levensbedreigende ziekten, en overig wetenschappelijk onderzoek.

Kenmerken van een infectieziekte die de volksgezondheid bedreigt, zijn:

- *Hoge besmettelijkheid*: De ziekte kan gemakkelijk van mens tot mens, van dier tot dier, van dier tot mens en andersom, worden overgedragen waardoor snelle verspreiding mogelijk is.
- *Potentieel voor ernstige gevolgen*: De ziekte kan leiden tot ernstige gezondheidscomplicaties, waaronder ziekenhuisopname, blijvende schade of overlijden.
- *Bepaalde of geen immuniteit in de bevolking*: Mensen hebben weinig of geen immuniteit tegen de veroorzakende ziekteverwekker, wat kan bijdragen aan de snelle verspreiding van de infectie.

- *Maatschappelijke ontwrichting*: De ziekte kan leiden tot verstoring van normale maatschappelijke activiteiten, waaronder gezondheidszorgsystemen, economieën en het dagelijks leven. Dit hoeft geen natuurlijke oorzaak te hebben, maar de ontwrichting door een infectieziekte kan ook beoogd worden door een vijandige actor.

Bij wetenschappelijk onderzoek naar infectieziekten spelen NHP's volgens sommigen een cruciale rol, omdat het immuunsysteem van NHP's het best vergelijkbaar is met dat van de mens waardoor ze het meest geschikt worden geacht voor het testen van vaccins en medicatie. NHP-onderzoek wordt uitgevoerd in de preklinische fase van vaccinontwikkeling, waarbij de veiligheid en effectiviteit van kandidaatvaccins worden onderzocht voordat deze op mensen worden getest.

Onderdeel van de opdracht van de commissie is ook om te “kijken naar de strategische Europese autonomie en (vermindering van de) afhankelijkheid van andere landen daar waar het bijvoorbeeld gaat om vaccinontwikkeling.” De vraag naar strategische autonomie speelt bij NHP-onderzoek vooral bij de bestrijding van pandemische infectieziekten en de ontwikkeling van vaccins. De belangrijke rol die Nederlandse onderzoekers hebben gespeeld bij de identificatie van het coronavirus en de vaccinontwikkeling deden zij weliswaar in grote internationale samenwerkingsverbanden, maar konden zij alleen doen op basis van hun eigen onderzoekservaring, met hun Nederlandse onderzoekfaciliteiten en kapitaliserend op hun internationale naam en faam. Op dit moment—volgens de virologen die de commissie gesproken heeft—zijn NHP's nog steeds noodzakelijk bij onderzoek naar nieuwe infectieziekten die de volksgezondheid bedreigen. Een Nederlandse NHP-faciliteit draagt daarom bij aan strategische autonomie in het geval zich weer een nieuwe pandemie zou voordoen. Dit betekent niet dat het onmogelijk is om nu het NHP-onderzoek af te bouwen, maar de commissie benoemt de resulterende grotere afhankelijkheid van het buitenland wel als een risico; en bij weging van dat risico dienen ook de huidige grillige ontwikkelingen in geopolitieke relaties binnen Europa en met de VS, Rusland en China in beschouwing genomen te worden.

Het begrip 'levensbedreigende ziekte' wordt vooral gehanteerd in het politieke debat. In de wetenschappelijke en klinische praktijk kan het echter niet scherp worden afgebakend. Na een gedetailleerde analyse concludeert de commissie dat 'levensbedreigend' als karakterisering van ziekte onvoldoende wetenschappelijk onderbouwd kan worden en dus niet kan worden gehanteerd als criterium voor de toelating van NHP-onderzoek. De commissie zal daarom in het vervolg van haar onderzoek spreken over 'levensbedreigende en anderszins ernstige ziekten'. Dit impliceert dat bij toepassing van dit criterium een politieke keus gemaakt moet worden over waar de 'knip' wordt gemaakt tussen meer en minder ernstig, tussen ziektes waarvoor wel en waarvoor niet NHP-onderzoek wordt toegelaten.

Het overig wetenschappelijk onderzoek met niet-humane primaten omvat vooral fundamenteel wetenschappelijk onderzoek, maar overlapt deels met de vorige categorie van onderzoek naar levensbedreigende en anderszins ernstige ziekten. Te denken valt aan allerlei neurowetenschappelijk onderzoek, zoals naar de ziekte van Parkinson, en aan onderzoek naar kanker, gendefecten, hart- en vaatziekten en diabetes.

Uit de analyse van de internationale literatuur blijkt dat Nederland een belangrijke uitvoerder van NHP-onderzoek is. Nederland staat op de achtste positie als het gaat om grootste uitvoerders van NHP-onderzoek wereldwijd, gemeten naar aantallen publicaties. Nederland is een belangrijke

bijdrager aan NHP-onderzoek binnen de EU—bijvoorbeeld betrokken bij 64% van het gepubliceerde NHP-onderzoek in de EU in 2021.

Vertaalbaarheid van NHP-modellen

Er zijn verschillende bronnen die aangeven dat NHP-onderzoek nog steeds een belangrijk model is voor onderzoek naar zowel infectieziekten als levensbedreigende en anderszins ernstige ziekten bij de mens. NHP-onderzoek wordt nog steeds veel toegepast waar de complexiteit van de menselijke biologie en ziekteprocessen moeilijk in andere modellen te reproduceren zijn en waar ethische en praktische overwegingen direct menselijk onderzoek beperken. Voor het testen van de veiligheid en werkzaamheid van nieuwe medicijnen en behandelingen worden NHP's vaak noodzakelijk geacht om te voorspellen hoe mensen zullen reageren op die medicijnen of behandelingen. Tegenstanders van NHP-onderzoek richten een belangrijk deel van hun kritiek op deze argumentatie: zij betogen dat er steeds meer aanwijzingen zijn dat de vertaalbaarheid van NHP-modellen naar de mens tekortschiet.

Sommige gesprekspartners geven aan dat er behoefte is aan meer onderzoek naar de vertaalbaarheid van NHP-modellen naar de mens. Wanneer zijn proeven op NHP's echt noodzakelijk om veilig en effectief gebruik bij mensen aan te tonen? Wanneer kunnen proeven op kleine dieren of alternatieven voor dierproeven volstaan? En geven deze alternatieven dan voldoende inzicht in de effecten op mensen? Anderen betogen dat er ziekten zijn waarvoor NHP's nog duidelijk het beste model zijn—bijvoorbeeld wanneer het systemische effecten op verschillende orgaansystemen betreft. Daarnaast is de vertaalbaarheid van zelfs de best beschikbare diermodellen (inclusief de mens) nooit perfect, wat leidt tot vragen over de noodzaak van diermodellen in het algemeen, maar ook over de vertaalbaarheid van andere modellen—belangrijke discussies die echter buiten de taakstelling van de commissie vallen.

NAM's

NAM's omvatten onderzoek met menselijk weefsel, stamcellen, celweeksystemen, computermodellen en data-analyse. NAM's worden niet alleen ontwikkeld om dierproeven te vervangen, maar kunnen ook los daarvan bijdragen aan het begrip van humane ziektemechanismen en het effect van chemische stoffen op humane cellen en weefsels.

Belangrijke groepen NAM's zijn:

- *Organ-on-a-chip*: miniatuurmodellen van menselijke organen die bepaalde fysiologische processen kunnen modelleren;
- *Organoiden en celweekmodellen*: 3D-celstructuren die menselijke weefsels modelleren;
- *Computermodellen en kunstmatige intelligentie*: geavanceerde simulaties van biologische processen en big-data analyses van grote bestanden.

Strikt genomen worden 'Controlled Human Infection Models' (CHIM's) en *systematische literatuuranalyses* niet tot NAM's gerekend, maar omdat ze beide tot een belangrijke reductie in NHP-proeven kunnen leiden, worden ze wel door de commissie besproken.

Er zijn verschillende manieren waarop NAM's een alternatief voor proeven op NHP's zouden kunnen vormen. Een eerste voordeel van NAM's is dat zij inzicht kunnen geven in effecten en risico's van een behandeling waardoor met meer vertrouwen die behandeling direct op mensen kan worden toegepast zonder eerst experimenten met NHP's te doen. Ten tweede kunnen NAM's in sommige gevallen zelfs beter inzicht geven in de effecten en risico's van behandelingen dan experimenten met NHP's. Ten derde kunnen NAM's meer scherpte brengen in de keuze tussen verschillende dierproefmodellen als toch een dierproef noodzakelijk is. Als laatste kunnen NAM's, doordat zij vaak

enkelvoudige orgaanmodellen betreffen, preciezere informatie geven over de behandeling, waardoor de onderzoeker de onderzoeksvraag kan aanscherpen of de behandeling kan verbeteren voordat onderzoek op NHP's of mensen volgt. Hierdoor kan de belasting op NHP's lager zijn of kunnen er minder of geen NHP's nodig zijn.

Omdat een dierproef en een NAM nooit precies hetzelfde meten, kunnen dierproeven niet zomaar één op één door NAM's vervangen worden. De onderzoeksvraag moet hierbij leidend zijn, en vaak is een combinatie van NAM's het alternatief. Die onderzoeksvraag moet het beginpunt in het ontwikkel- en implementatietraject van NAM's zijn. Daarbij speelt de voorziene 'gebruikscontext' een essentiële rol.

De diversiteit in NAM's en het brede scala aan onderzoeksvragen en gebruikscontexten betekenen dat een directe vergelijking tussen de inzet van NAM's en NHP-experimenten moeilijk te maken is. Wel zien onderzoekers veelbelovende NAM's die binnen korte of langere termijn de NHP-experimenten voor een gedeelte kunnen vervangen (zie [tabel 4](#) in het rapport). NHP-experimenten kennen, in vergelijking met veel NAM's, belangrijke beperkingen in hun kwalificatie voor mens-relevante gebruikscontexten. Op dit moment zijn NAM's echter nog niet in staat om alle onderzoeksvragen te beantwoorden waarvoor NHP-experimenten nodig worden geacht.

Ook bij regelgevende instanties is veel aandacht voor de vermindering en vervanging van dierproeven in het algemeen en NHP-experimenten in het bijzonder. Een extra aanleiding voor deze aandacht vormt het wereldwijde tekort aan NHP's tijdens de SARS-CoV-2-crisis. EMA en CBG stimuleren dat NAM-onderzoekers in een zo vroeg mogelijk stadium contact zoeken met de regelgevende instanties. Zo kan het hele traject van NAM-ontwikkeling en -implementatie beginnen met een heldere probleemstelling, 'fit for purpose' en 'context of use', en wordt de kans op acceptatie door EMA en CBG groter.

Vier beleidsscenario's

Dit rapport bestaat uit twee delen. In deel 1 rapporteert de commissie de resultaten van haar onderzoek naar wat wel en niet kan met betrekking tot de vermindering van NHP-proeven. In deel 2 presenteert de commissie vier beleidsscenario's. Op deze manier beantwoordt de commissie aan haar opdracht om onderzoek te doen naar wat kan en niet kan, zonder zelf een beleidsadvies te geven (zie [tabel 5](#) voor een overzicht).

In deel 1 behandelt de commissie een aantal deelvragen: over de historische en maatschappelijke achtergrond van NHP-experimenten, de mogelijke ethisch-filosofische kaders, de relevante nationale en internationale wet- en regelgeving, de Nederlandse NHP-faciliteiten, de aantallen NHP-experimenten in Nederland, en veel aspecten van internationaal NHP-onderzoek.

Over het antwoord op een aantal andere belangrijke deelvragen blijkt echter geen wetenschappelijke consensus te bestaan. Dit betreft met name: de vertaalbaarheid van NHP-experimenten, het belang van NHP-experimenten voor verschillende wetenschapsgebieden, de vooruitzichten in de ontwikkeling van NAM's, en de vraag welk ethisch kader het meest adequaat is. De commissie geeft in die gevallen een zo compleet mogelijk beeld van de verschillende en vaak tegengestelde antwoorden op dergelijke deelvragen.

Op deelonderwerpen waarover geen wetenschappelijke consensus bestaat, kan de commissie geen eenduidig advies geven. Op die deelonderwerpen zijn dus politieke en beleidsmatige keuzes noodzakelijk, waarbij wel de wetenschappelijke analyse wordt meegewogen maar waarbij deze analyse geen doorslaggevende grondslag biedt voor de keuze. Daarom werkt de commissie in deel 2 van het rapport vier beleidsscenario's uit voor mogelijke toekomstige ontwikkelingen in het gebruik van NHP's. Indachtig de opdracht om *geen* beleidsadvies te geven, presenteert de commissie deze beleidsscenario's zo evenwichtig en neutraal mogelijk—zij heeft geen eigen voorkeur.

De beleidsscenario's hebben ook veel gemeenschappelijk. De commissie formuleert daarom een aantal conclusies die voor alle beleidsscenario's gelden. Deze gaan over:

- De rol van DEC's en CCD en hun reflectie op de schade-baten analyse
- Het belang van NAM-onderzoek
- De proactieve rol van regelgevende instanties zoals EMA en CBG
- Het belang van de streefbeeldbenadering: voor NHP-onderzoek zijn vooral de streefbeelden hersenonderzoek, immunologie en infectieziekteonderzoek van belang
- Het belang van Europese coördinatie en samenwerking in NAM- en NHP-onderzoek
- Het belang van systematische literatuuranalyses
- Transparantie in de overheidscommunicatie over gemaakte beleidskeuzes
- De noodzaak alle NHP-onderzoek volgens de ARRIVE-richtlijnen te publiceren

Beleidsscenario 1: Afbouw NHP-onderzoek in Nederland

In beleidsscenario 1 besluit de Nederlandse overheid te stoppen met het financieren van het BPRC. De bestaande onderzoeken op NHP's worden afgebouwd en daarna stopt publieke financiering van het BPRC als onderzoeksfaciliteit en van NHP-onderzoek. Voldoende financiering blijft nog wel nodig om het BPRC in staat te stellen de apen tijdens hun 'pensionering' goed te huisvesten—totdat de laatste aap overleden is.

Een belangrijke overweging bij dit besluit is dat sommigen van oordeel zijn dat onderzoek met NAM's en onderzoek direct op de mens voldoende perspectief bieden op hoge wetenschappelijk kwaliteit zonder NHP's, omdat de NHP-modellen minder goed vertaalbaar zijn naar de mens dan vaak wordt aangenomen. Daarmee is overigens niet iedereen het eens. Veel onderzoekers, waaronder ook NAM-onderzoekers, zien het NHP-model nog steeds als een noodzakelijk element in onderzoek naar infectieziekten en levensbedreigende en anderszins ernstige ziekten. In hun ogen is dus een implicatie van dit beleidsscenario dat onderzoek naar infectieziekten en levensbedreigende en anderszins ernstige ziekten in Nederland juist aan kwaliteit inboet.

Dit scenario kan binnen twee verschillende ethische kaders verdedigd worden. Ten eerste een deontologisch kader waarbij mensen als gelijkwaardig aan NHP's worden gesteld en dus het gebruik van NHP's ten behoeve van mensen niet acceptabel is. Maar ook binnen een utilistisch ethisch kader is dit beleidsscenario verdedigbaar indien de baten van het NHP-onderzoek niet opwegen tegen de schade bij de NHP's.

In dit beleidsscenario is het overigens nog steeds mogelijk dat organisaties (bedrijven, universiteiten en zelfs het BPRC zonder overheidsfinanciering) in Nederland NHP-onderzoek uitvoeren, mits goedgekeurd door de CCD.

Samenvatting van opbrengst, verlies en risico

De *opbrengst* van dit beleidsscenario is dat het onderzoek in Nederland met NHP's wordt afgebouwd. (Voorbehoud: deze afbouw geldt primair voor het NHP-onderzoek in het BPRC, want programma's in andere instituten zoals het NIN en farmaceutische bedrijven kunnen niet direct door de Nederlandse

overheid worden aangestuurd.) Het *verlies* dat Nederland in dit beleidsscenario moet accepteren is dat het helemaal afhankelijk wordt van het buitenland voor onderzoek met NHP's. Nederland komt daardoor in de ethisch lastige positie dat het niet zelf NHP-onderzoek doet maar nog wel gebruik maakt van medische innovaties, zoals bijvoorbeeld vaccins en geneesmiddelen, die met NHP's in het buitenland ontwikkeld zijn. Een tweede *verlies* is de grotere afhankelijkheid van buitenlands NHP-onderzoek waardoor Nederland minder goed kan reageren op een nieuwe pandemie. Een eerste *risico* is dat Nederland niet meer zelf de kwaliteit van NHP-faciliteiten kan monitoren. Een tweede *risico* is dat goede onderzoekslijnen die NHP's gebruiken in het buitenland worden voortgezet, waarmee Nederland kennis en ervaring verliest.

Beleidsscenario 2: Vermindering NHP-onderzoek in Nederland

In beleidsscenario 2 besluit Nederland minder NHP-onderzoek via het BPRC te financieren, maar niet volledig af te bouwen. De overweging hierbij is dat voor onderzoek naar infectieziekten en sommige levensbedreigende en anderszins ernstige ziekten het gebruik van NHP's nog steeds noodzakelijk is.

Deze beleidskeuze steunt op de overtuiging dat NAM's nog niet voldoende beschikbaar zijn en dat NHP-modellen voldoende vertaalbaar zijn naar de mens en daarom een belangrijk element zijn in het onderzoek ten behoeve van de bestrijding van infectieziekten die een bedreiging voor de volksgezondheid vormen en ten behoeve van onderzoek naar sommige levensbedreigende en anderszins ernstige ziekten. Niet iedereen deelt overigens deze overtuiging: er is ook NHP-onderzoek, betogen deze critici, waarbij die vertaalbaarheid onvoldoende duidelijk is.

Ethisch stoelt dit beleidsscenario op de opvatting dat de mens moreel hoger staat dan het dier en dat dieren mogen worden gebruikt ten behoeve van mensen als er zwaarwegende belangen voor de mens op het spel staan.

Dit beleidsscenario kan via twee verschillende sub-scenario's gerealiseerd worden door de manier waarop voorwaarden worden gesteld aan de overheidsfinanciering van het BPRC. De sub-scenario's verschillen in de manier waarop de vermindering tot stand komt. In sub-scenario **2a** wordt alleen onderzoek toegestaan naar infectieziekten die de volksgezondheid bedreigen. In sub-scenario **2b** wordt bovendien onderzoek toegestaan naar een select aantal nader te specificeren levensbedreigende en anderszins ernstige ziekten. Dit betekent dat een beleidskeuze moet worden gemaakt over waar de 'knip' tussen wel en niet toegestane NHP-experimenten komt te liggen.

Samenvatting van opbrengst, verlies en risico

De eerste *opbrengst* van dit beleidsscenario is dat het onderzoek in Nederland met NHP's substantieel wordt verminderd (met hetzelfde voorbehoud over NIN en industrie als bij het eerste beleidsscenario). Een tweede *opbrengst* is dat Nederland een eigen faciliteit en capaciteit behoudt om bij te dragen aan vaccinontwikkeling en zo zijn pandemische weerbaarheid op peil houdt. Het BPRC behoudt een kolonie NHP's en blijft onderzoek doen naar infectieziekten die de volksgezondheid bedreigen om de faciliteiten en vaardigheden voor die pandemische vaccinontwikkeling op peil te houden. Het *verlies* dat Nederland in dit beleidsscenario accepteert is dat sommige andere NHP-onderzoekslijnen worden afgebouwd, afhankelijk van de keuzes tussen en binnen de sub-scenario's. Nederland komt daardoor in de ethisch lastige positie dat het bepaald NHP-onderzoek niet zelf doet maar nog wel gebruik maakt van medische innovaties, zoals bijvoorbeeld vaccins en geneesmiddelen, die met NHP's in het buitenland ontwikkeld zijn. Verder betekent dit een *risico* dat goede onderzoekers naar het buitenland vertrekken, waarmee Nederland kennis en ervaring verliest. Een tweede *risico* van minder NHP's is dat bepaalde onderzoeken niet meer uitgevoerd kunnen worden onder andere vanwege de beperkte beschikbaarheid van NHP's of een te lage statistische power.

Beleidsscenario 3: Behoud van NHP-onderzoek in Nederland

In beleidsscenario 3 besluit Nederland het huidige onderzoek met NHP's te behouden. De belangrijkste overweging is dat zo maatschappelijke schade wordt voorkomen door onderzoek te blijven doen naar infectieziekten die de volksgezondheid bedreigen, naar behandelingen tegen levensbedreigende en anderszins ernstige ziekten en mogelijk naar hersenaandoeningen (mede afhankelijk van KNAW-beleid).

Nog steeds wordt in dit beleidsscenario ook nadruk gelegd op de wettelijk vereiste 3V-benadering: vervanging, vermindering en verfijning van NHP-experimenten. De focus ligt hierbij op het nog verder verbeteren van dierenwelzijn en het uitvoeren van systematische literatuuranalyses voor een betere wetenschappelijke verantwoording van het gebruik van NHP's.

NHP-onderzoek wordt nog steeds essentieel geacht voor bepaalde wetenschappelijke vraagstukken, vooral op het gebied van infectieziekten, immunologie en neurowetenschappen. Het is in principe wel mogelijk dat de criteria in de schade-batenanalyse door DEC's en CCD worden aangepast.

Samenvatting van opbrengst, verlies en risico

De *opbrengst* van dit beleidsscenario is dat het huidige onderzoek naar infectieziekten die de volksgezondheid bedreigen en naar levensbedreigende en anderszins ernstige ziekten kan doorgaan. Het *verlies* dat Nederland in dit beleidsscenario accepteert is dat er geen vermindering van NHP-onderzoek plaatsvindt. Daarmee heeft dit beleidsscenario het *risico* dat onvoldoende wordt rekening gehouden met maatschappelijke onvrede over het voortbestaan van NHP-onderzoek.

Beleidsscenario 4: Mogelijke toename NHP-onderzoek in Nederland

In beleidsscenario 4 wordt een toename van NHP's en NHP-experimenten in Nederland eventueel toegelaten indien NAM's onvoldoende de gestelde onderzoeksvragen kunnen beantwoorden. Een belangrijke overweging is dat het gebruik van NHP's een grote rol kan spelen in de bestrijding van infectieziekten die de volksgezondheid bedreigen, bij de behandeling van levensbedreigende en anderszins ernstige ziekten en bij fundamenteel onderzoek. Kritiek op de vertaalbaarheid van NHP-experimenten wordt onderkend, maar met meer systematische literatuuranalyses wordt getracht te voorkomen dat experimenten worden gedaan die, gezien de resultaten van eerder onderzoek, weinig kans op slagen hebben of overbodig zijn. Het is in dit beleidsscenario overigens ook mogelijk dat het aantal NHP-experimenten *niet* toeneemt indien voldoende NAM's beschikbaar komen of indien op Europees niveau voor vestiging van een centrale faciliteit in een ander land wordt gekozen.

Essentieel in dit scenario is dat Nederland in Europa pleit voor het centreren van alle NHP's in één primatencentrum. Het BPRC zou hiervoor een kandidaat zijn omdat het op dit moment al een vooraanstaande en hoogkwalitatieve rol speelt op het gebied van NHP-fok, -huisvesting en -onderzoek. Dit zou dan leiden tot toename van het aantal gehuisveste NHP's in Nederland, maar zou een vermindering van het totale NHP-gebruik in Europa tot gevolg moeten hebben. Nederland neemt aldus de ethische last van het houden van NHP's voor andere landen in Europa op zich. Een scenario waarbij alle NHP's in Europa gecentraliseerd zouden worden, vergelijkbaar met strategieën zoals deze succesvol zijn gebleken in onderzoekscentra op het gebied van de ruimtevaart en de elementaire-deeltjes fysica, impliceert ook dat een dergelijk centrum in een ander land dan Nederland gevestigd zou kunnen worden, waarmee de verschillende overwegingen op nationaal, Nederlands niveau anders worden.

Samenvatting van opbrengst, verlies en risico

De *opbrengst* van dit beleidsscenario is dat naast het huidige onderzoek naar infectieziekten die de volksgezondheid bedreigen en naar levensbedreigende en anderszins ernstige ziekten nog ander

NHP-onderzoek mogelijk wordt. Een daarvoor benodigde toename van het aantal NHP-experimenten is in dit beleidsscenario toegelaten, maar niet noodzakelijk—het is immers ook mogelijk dat met in de nabije toekomst ontwikkelde NAM's de onderzoeksvragen ook kunnen worden beantwoord. Het *verlies* dat Nederland in dit beleidsscenario accepteert is dat op Nederlandse bodem geen vermindering van NHP-onderzoek plaatsvindt, terwijl daar ethisch goede redenen voor kunnen zijn. Daarmee heeft dit beleidsscenario het *risico* dat onvoldoende wordt rekening gehouden met maatschappelijke onvrede over het bestaan van NHP-onderzoek.

Lists

Abbreviations

3Rs (3Vs)	Reduce, refine and replace (<i>verminderen, verfijnen en vervangen</i>)
AI	Artificial intelligence
AIDS	Acquired Immune Deficiency Syndrome
ALURES	Animal Use Reporting EU System: database of animal research – part 1 detailing numbers of studies, part 2 detailing purposes of studies, part 3 detailing genetically modified laboratory animals
BPRC	Biomedical Primate Research Centre
BSL	Biosafety Level
MEB	Medicines Evaluation Board
CCD	Central Committee on Animal Experiments
CCMO	Central Committee on Research Involving Human Subjects
CHIM	Controlled Human Infection Model
Cib	Centre for infectious disease control
CABT	Centre for Animal-free Biomedical Translation
DEC	Animal Experiments Committee
ECHA	European Chemicals Agency
EMA	European Medicines Agency
EPAA	European Partnership for Alternative Approach to Animal Testing
EU	European Union
FDA	Food and Drug Administration (US)
HIV	Human immunodeficiency virus
ICH	International Council for Harmonisation
Establishment order	Order of the Minister of OCW of 5 December 2023, no. OWB/42696432 establishing the Committee to investigate ways to reduce the number of experiments on non-human primates
IvD	Animal Welfare Authority
KNAW	Royal Netherlands Academy of Arts and Sciences
Minister/Ministry of LVVN	Minister/Ministry of Agriculture, Fisheries, Food Security and Nature
Minister/Ministry of OCW	Minister/Ministry of Education, Culture and Science
NAM	New approach methodology (method that serves as an alternative to animal research)
NCad	National Advisory Committee on Animal Research Policy
NHP	Non-human primate
NIH	National Institutes of Health (US)
NIN	Netherlands Institute for Neuroscience, KNAW
NTS	Non-Technical Summary
NVWA	Netherlands Food and Consumer Product Safety Authority
NWO	Dutch Research Council (Netherlands Organisation for Scientific Research)
OECD	Organisation for Economic Co-operation and Development
PETA	People for the Ethical Treatment of Animals
PMDA	Pharmaceutical and Medical Devices Agency (Japan)
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2

SCHEER	Scientific Committee on Health, Environmental and Zoonotic Risk
TNO	Netherlands Organisation for Applied Scientific Research
TPI	Animal-Free Innovation Transition Programme
Wod	Animal Experiments Act
ZonMw	Research-funding organisation formed by merger of ZorgOnderzoek Nederland (ZON) and the Medical Sciences (MW) domain of NWO

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Introduction

In November 2022, the House of Representatives asked the government to investigate ways of reducing the number of experiments on non-human primates (NHPs).¹ In response, in December 2023, the Minister of Education, Culture and Science (OCW) established a committee to carry out the investigation, as detailed in the following section. The committee was tasked with investigating the possibility of further reducing the number of experiments with NHPs without affecting the research strictly necessary to control life-threatening diseases and outbreaks of infectious diseases that threaten public health.

The permissibility, utility and necessity of NHP research is a complex field, because it involves matters of animal ethics, society's pandemic preparedness, medical research, vaccine and medicine development and production, international regulations and geopolitical relations. Policy decisions concerning such a complex field should be based on the best possible information, drawing on scientific research, the legal and regulatory parameters and the societal context. In this report, the committee describes all aspects of this field as completely as possible. As will become clear, there is no scientific consensus on all aspects: policy choices will therefore have to be made that balance these various perspectives as well as possible.

The committee has not carried out any new scientific research; it has described the scientific status quo and the viewpoints within society concerning all matters pertinent to the question of how the number of NHP experiments could be reduced without affecting research that is strictly necessary for the control of life-threatening illnesses and outbreaks of infectious diseases that threaten public health. The committee's problem analyses of the field, of the interrelationships between the various aspects, and of the possible policy options were performed in accordance with good scientific practice. The quality of those analyses was assessed by international peer review.

The committee was not asked to give policy advice, but to "investigate what can and cannot be done".² This report is therefore in two parts. In the first part, the committee describes the results of its "investigation of what can and cannot be done"; in the second part, the committee presents four distinct policy scenarios. Each of the four scenarios is the result of a different weighting of scientific arguments. The committee does not express its own preference for any of the policy scenarios. That does not mean, however, that the findings are colourless. On several points, the committee formulates clear conclusions, which apply to all policy scenarios.

Assignment

The assignment given to the NHP Research Committee derives from the motion proposed to the House of Representatives by Member Wassenberg and passed unanimously on 24 November 2022. In a letter to Parliament on 6 July 2023, the Minister of OCW outlined how he intended to implement

¹ Tweede Kamer, Motie van het lid Wassenberg c.s. over een onderzoek naar de mogelijkheid om het aantal proeven op niet-humane primaten verder te verlagen [House of Representatives, Motion by Member Wassenberg et al. regarding research into the possibility of further reducing experiments on non-human primates].

² Minister of OCW, Voortgang onderzoek verdere verlaging proeven op niet-humane primaten (motie Wassenberg c.s.) [Progress of research into the further reduction of experiments on non-human primates (motion by Wassenberg et al.)].

the motion.³ On 5 December 2023, the minister signed the order establishing the committee, which was published in the Government Gazette on 5 February 2024.⁴ (See Appendix 5 for details.)

The main question the committee was asked to address was whether the number of experiments on NHPs could be reduced without affecting the research strictly necessary to control life-threatening illnesses and outbreaks of infectious diseases that threaten public health.

That question was elaborated in the establishment order, which defined several subtasks (see also [Appendix 5](#)):

1. The committee is to define the terms 'life-threatening disease' and 'infectious disease that threatens public health'.
2. The committee is to consider what scientific research with NHPs is needed to control life-threatening diseases and outbreaks of infectious diseases that threaten public health, and the circumstances under which such research could be further reduced in the future.
3. The committee is to explore the options for entirely phasing out other scientific research with NHPs as soon as possible.
4. The committee is to map the options referred to in the previous subtask by defining various scenarios in which the scientific, ethical, legal, economic, international and societal implications are set out.

In its problem analysis, the committee identified several sub-questions, which include:

- What is the historical background to the use of NHPs and the public debate regarding their use?
- Where in the Netherlands does NHP research take place?
- What does the international field of NHP research look like?
- How does NHP research in the Netherlands compare with NHP research in other countries?
- What do NHP research practices in the Netherlands look like?
- What ethical frameworks can be used to appraise the use of NHPs for scientific research, and what conclusions does such appraisal lead to?
- What are life-threatening diseases and what are infectious diseases that threaten public health?
- What kinds of scientific research are NHPs used for?
- How useful and how necessary is NHP research?
- How relevant is NHP research to scientific knowledge regarding humans (i.e. how translatable is NHP research)?
- What legislative, regulatory and medicine licensing frameworks have a bearing on NHP research?
- What financial and economic significance does NHP research have?
- What are the options for reducing and phasing out NHP research?
- What alternatives to animal research in general and to NHP research in particular ('new approach methodologies', or NAMs) are under development, and what can be expected from such alternatives?
- What are the geopolitics of NHP research, such as the Netherlands' increased or decreased dependence on other countries?
- What European developments should the Netherlands take into account?

³ Minister of OCW.

⁴ Minister of OCW, Instellingsbesluit Commissie onderzoek niet-humane primaten [Order Establishing the Committee on Research Involving Non-Human Primates].

The committee's answers to those sub-questions are presented in Part 1 of this report. In Part 2, as indicated earlier, the committee translates those answers into four policy scenarios.

Make-up of the Committee

The members of the committee are listed in the government order establishing the committee (see [Appendix 5](#)).⁵ The committee's collective expertise was sufficiently wide to enable it to fulfil its task. A brief profile of each committee member is presented below.

- Prof. W.E. (Wiebe) Bijker, chair, Emeritus Professor of Science, Technology and Society Studies – expert on the interactions between science, technology and society
- Prof. A. (Annemieke) Geluk, immunologist and chemist – expert on mycobacterial infectious diseases, experience in both immunological animal research and clinical trials
- Prof. W.A. (Pim) van Gool, neurologist – experience in clinical scientific research, animal experimental neuroscience research and scientific advice for policy purposes
- Dr. L. (Lotte) Krabbenborg, sociologist – expert on interactions between science and society
- Prof. H.G.M. (Bert) Leufkens, Emeritus Professor of Medicine Policy and Regulation – former chair of the Medicines Evaluation Board (CBG)
- Prof. F.L.B. (Franck) Meijboom, ethicist – experience in theoretical background and practical ethical judgements concerning animal experiments and animal-free innovations
- Prof. C.L. (Christine) Mummery, developmental biologist – expertise in stem cell research and organ-on-chip models (NAMs), ethical discussion of NAM applications and scientific advice on public-private investments
- Prof. C.P. (Chantal) Rovers, internist-infectiologist – expertise on infectious disease outbreaks, clinical scientific research experience
- Dr. F.M.S. (Femke) de Vrij, neurobiologist – expert on stem cell models for brain diseases, experience in both experimental animal research (mouse models, xenotransplants) and NAMs (organ-on-chip and brain organoids)

Staff at Andersson Elffers Felix (AEF), a social issues agency (Jente Waal, Janneke Jansink and Sander Geurts) were assigned to the committee to assist with the investigation and writing of this report.

Methodology and work process

The committee followed the methodology used by most scientific advisory committees.⁶ Two types of information source were utilised: literature review and interviews with experts. In the committee's interpretation of information from both sources, the expertise of the committee's own members played an important role.

Hence, the committee did *not* investigate the views of the Dutch public, did *not* perform its own systematic literature review, and did *not* observe practices in laboratories where NHP research is performed.⁷ Such activities were not necessary for the committee to fulfil its task.

⁵ The published establishment order includes details of committee members' interests.

⁶ See, for example, regarding the Health Council of the Netherlands: Bijker, Bal, and Hendriks, *The Paradox of Scientific Authority*.

⁷ The systematic review is a well defined scientific means of addressing a research question by methodically analysing the findings of previous studies: Munn et al., 'Systematic review or scoping review?' Bramer et al., 'Optimal database combinations for literature searches in systematic reviews'. The value of a systematic review depends on the quality and completeness of the reviewed studies. In this context, the opportunities for publication via forms of open science are very useful. See, for example: UNESCO, 'UNESCO Recommendation on Open Science'.

The scientific literature selected for inclusion in the review was sufficiently wide to enable the committee to adequately address the questions it was constituted to answer. The selected literature included both literature on the history of animal research in general and literature on the current status of NHP research and possible ways of reducing it. The committee reviewed national and international scientific literature, policy documents and research reports. Additional literature was obtained from the experts consulted and during the international peer review (see below).

The experts consulted by the committee were selected with a view to ensuring that all relevant views on and experience with NHP research were covered (see [Appendix 2](#) for details). Almost all interviews were conducted by two or three committee members and an AEF staff member. To ensure continuity, the committee chair participated in almost all interviews. The committee followed a standard interview plan to ensure consistency while also allowing scope for the discussion of other topics. The committee made notes on the interviews, which were used when compiling this report. The committee has chosen not to quote what was said in interviews literally. The experts interviewed by the committee are not responsible for the contents of this report.

The committee conducted a working visit to the Biomedical Primate Research Centre (BPRC) in Rijswijk on 21st March 2024. During the visit, the committee spoke to BPRC staff and to the centre's current and future directors about the BPRC and how research with NHPs is conducted there. A delegation from the committee also paid a working visit to the Netherlands Institute for Neuroscience (NIN), the only other facility for NHP research in the Netherlands, on 12th April 2024.

On 16th July 2024, the committee organised a consultation meeting with researchers engaged in the development and application of 'new approach methodologies' (NAMs). On 30th August 2024, the committee organised a consultation meeting with representatives of groups involved in the public debate on conducting scientific experiments on NHPs. The proceedings of both consultations were used by the committee to refine its findings and elaborate various sections of this report. A list of participants in these consultations is attached to this report as [Appendix 3](#). The participants are not responsible for the contents of this report.

Finally, the committee commissioned an analysis of the international literature by bioinformatician Dr. James Gallant (Department of Anatomy and Embryology, LUMC). Dr. Gallant's analysis examined scientific publications regarding studies with NHPs, with the aim of clarifying the main characteristics of international NHP research. The analysis helped the committee to build a clear picture of international trends and developments in the use of NHP research, including the countries and centres where such research is done and its purposes. The study design and the results obtained are presented in [Appendix 1](#) to this report.

About this report

The committee was established by the Minister of OCW but carried out its work independently. The committee was guided by an interdepartmental consultation group made up of representatives from all relevant ministries and from the research councils ZonMw and NWO (see [Appendix 6](#)).

The Dutch draft version of the report was reviewed for factual inaccuracies by some of the expert interviewees prior to the international peer review. The issues they identified were subsequently addressed as far as possible.

The report was written in Dutch and then translated into English to enable international peer review. The committee reviewed the English translation and approved it for use in the peer review.

The committee uses Chicago Manual Style 2017, with abbreviated reference to the source in the footnotes. Full source references are given in the literature overview.

The draft report was reviewed for scientific quality by anonymous, international reviewers. Formally, the interdepartmental consultation group acted as the client for this peer review, which was conducted by ZonMw/NWO (see [Appendix 7](#)). Based on the anonymous reviews, the committee has made adjustments and improvements to certain aspects of the report (see [Appendix 8](#)).

PART I The scope for reducing research with non-human primates

1 Contextual discussion of NHP research

1.1 Social developments

The use of NHP experiments in scientific research and product development (medicines, vaccines) has been the subject of debate for many years. The term 'NHP' refers to primates that are not part of the *Homo sapiens* species (humans), such as great apes (chimpanzees, bonobos, gorillas, orangutans and gibbons), Old World monkeys (including rhesus monkeys), New World monkeys (including capuchin monkeys and Callitrichidae), tarsiers, and prosimians (lorises, galagos, and lemurs, including ring-tailed lemurs). With certain strict exceptions, research with great apes has been banned in the Netherlands and the rest of the EU since 2003.⁸ Research on NHPs, other than great apes, is allowed under strict conditions. In the Netherlands, NHP research involves only smaller monkeys, namely macaques (long-tailed macaques and rhesus monkeys) and marmosets (Callitrichidae).

Many researchers, companies and regulatory bodies consider NHP experiments necessary for good, reliable science that is also socially relevant. It is argued that research with NHPs, for example, has contributed to major medical breakthroughs, such as the development of vaccines and engineered (brain) implants. Others doubt the usefulness and necessity of NHP experiments and are critical of, for example, the translatability of NHP experiments to humans. Test laboratories and university researchers are actively developing new methods as alternatives to animal research in general and NHP experiments in particular. Such methods are referred to as 'NAMs'.

In society, the use of laboratory animals, and NHPs in particular, has long been a topic of debate. For example, anti-vivisection organisations have been established in several countries since the nineteenth century.⁹ The groups actively advocate the abolition of animal research, presenting arguments based on animal welfare, animals' moral status, low effectiveness and low translatability to human treatments. Other groups, such as some patient advocacy organisations, stress that abolishing all NHP research is not currently in their members' interest, although they support more research into alternative methods that could contribute to reducing the number of NHP experiments.

This brief outline of some of the scientific and societal debates on NHPs illustrates the complexity of the task given to this committee by the House of Representatives. The values and interests of very different parties must be considered, to allow an informed political choice.¹⁰

The committee has spent the past year exploring the NHP research landscape in order to identify the tensions that exist and understand the various points of view. The committee has built on previous studies and has added a consideration of the scope for NAMs replacing NHP research, and future development scenarios.¹¹ The committee has spoken with various relevant individuals and organisations, inventoried perspectives and explored dilemmas. In this report, the committee sets out its findings and presents four scenarios for the future use of NHPs.

⁸ For the history of chimpanzees in scientific research, see: Turner, 'The History of Chimpanzees in Biomedical Research'.

⁹ Veen, 'Of Mice, Monkeys, and Better Science'.

¹⁰ For a broad overview of the history and current use of NHPs in research, see: Prescott, 'Using Primates in Captivity'.

¹¹ See Rathenau Instituut, 'Van Aap naar beter. Een verkenning en dialoog over proeven met apen' ['From Primate to Wellness. An exploration of and dialogue regarding experimentation on primates'] and KNAW, 'Gebruik van niet-humane primaten (NHP) als proefdier. Nut of Noodzaak?' ['Use of Non-Human Primates (NHPs) as Laboratory Animals. Convenience of Necessity?'].

1.2 Historical developments

Before the introduction of the Animal Experiments Act (Wod) in 1977, experimental animal research in the Netherlands was barely regulated. The issue of human obligations *vis à vis* animals first came to the fore in 1881 when the criminalisation of animal cruelty was debated. Although animal cruelty was made criminal, laboratory animals fell outside this legislation because their welfare was entrusted to the care of researchers. Several attempts to regulate laboratory animal research, in 1907 and 1933 for example, did not result in legislation due to opposition from the medical profession, which feared that scientific progress would be impeded. Only in the 1960s was a serious proposal for a licensing system made. The historical developments are described in more detail in [Appendix 4](#).

The 1977 Wod was a milestone since it introduced a legal framework for animal experiments. Since then, animal research has been permitted only by licence. Ethical considerations have played an increasingly significant role since then, with emphasis on the three Rs: reduce, refine and replace animal research. (In Dutch, the three Rs are three Vs: *verminderen*, *verfijnen* and *vervangen*.) European regulations such as the 1986 Directive 86/609/EEC and subsequent reviews emphasised the importance of ethical review but also showed that the system and enforcement could be improved. In the 1990s and 2000s, Dutch law was further tightened with, for example, a ban on animal research to test cosmetics and a complete ban on research using great apes.

Since 2014, regulations have been tightened with the implementation of the European Directive 2010/63/EU, and the Netherlands has set ambitious goals with a view to taking an international lead in the development and implementation of animal-free alternatives. The directive harmonises policy on animal research within Europe, meaning that the Netherlands cannot develop stricter policies than the other EU member states. However, the Netherlands is allowed to retain any pre-existing policy that goes further than the European policy. The Animal-Free Innovation Transition Programme (TPI Programme), established in 2017 by the Ministry of Agriculture, Fisheries, Food Security and Nature (LVVN, formerly LNV) as a partner programme in which the government and other organisations work together to accelerate the transition to animal-free innovation, supports that ambition. Although laboratory animals once again proved important for vaccine development during the coronavirus pandemic, the Dutch government remains committed to reducing animal research, with the aim of making the Netherlands a catalyst for international animal-free innovation.

1.3 Ethical-philosophical context

In order to assess the necessity of using animals in general and NHPs in particular for scientific research – and to assess the scope for phasing out animal and NHP research – it is necessary not only to consider the scientific justification for such research, but also to make certain moral judgements: what do we consider valuable, good and important? That is the field of ethics. Every opinion in the debate on the use of NHPs as laboratory animals goes hand in hand with value judgements and views regarding:

- the intrinsic value of animals,
- the value of human goals,
- how those different values should be weighed up against each other.

That ethical context is important in underpinning choices about the future of NHP research.

The value of animals

Animals are valuable to humans. That is often why animals are used in research: they can be a source of information that is relevant to scientific progress and human health. That usefulness can be an important argument for treating animals with care, just as one uses valuable utensils with care.

Instrumental use of animals can also lead to criticism of the use of NHPs if the studies in question do not lead to useful results. In such circumstances, NHPs are regarded as the wrong 'tool'.

The Wod gives another reason, besides their usefulness, for regarding animals as valuable: their intrinsic value. In other words, animals have a value independent of their usefulness or utility to humans. Even if an NHP is not used for an experiment, it has value. The recognition that animals have intrinsic value is based on various considerations. Assignment of intrinsic value is often linked to an animal having the capacity to experience suffering.¹² That aligns with Bentham's vision of the unique role of the capacity to experience suffering as a criterion for having value in moral society.¹³ On the basis of that criterion, NHPs have moral value in their own right, quite apart from any value they may have to humans. In that context, the empirical observation that animals have central nervous systems can be used to argue that animals have the capacity to suffer both physically and mentally, just as humans do. It can also be assumed that animals have an interest in avoiding pain and suffering, just as humans do. It therefore follows that suffering should never be inflicted needlessly on animals any more than on humans.

Although that vision is widely shared, there are other lines of theoretical reasoning. One is that the capacity to experience suffering is too broad a criterion, and that the minimum basic condition for the attachment of moral value is the capacity for rational action. On that basis, an animal deserves respect because it possesses certain mental characteristics, such as consciousness, awareness of time and the capacity for intentional action.¹⁴ Within that vision, NHPs form a special case because they satisfy the criterion of rationality, implying that they have inherent value that must be taken into account in moral judgements. At the opposite end of the continuum are theories that consider the capacity to experience suffering to be too strict a criterion. Proponents of such theories argue that all living things that are capable of flourishing have intrinsic value and should therefore be afforded respect in their own right. There are also theoretical views that claim that the capacity to experience suffering is too limited a criterion because, for example, it disregards the importance of the context in which an animal lives, or of the relationship between an animal and humans. Viewed from those perspectives too, NHPs may be regarded as animals with intrinsic moral value, to which we may have certain obligations.

Do all animals have equal value?

Animal research is carried out on a variety of species: from zebrafish to dogs and from mice to monkeys. However, research involving certain species provokes more discussion and opposition than research involving other species. That is certainly the case where research on NHPs is concerned. The Wod makes no significant distinction between the types of animal it covers – the same rules apply in relation to chickens, dogs and fish. However, additional conditions apply to NHP research. All animals can experience pain and thus their interests could be harmed in an animal experiment. It could therefore be argued that focusing particular attention on NHPs is arbitrary or even inconsistent. Moreover, the number of NHPs used for research is very small compared with the total number of animals used (see 2.4.2). Nevertheless, there are ethical arguments to support paying particular attention to NHPs. The starting point for such arguments is the level of cognitive development exhibited by NHPs and hence the extent to which their interests may be harmed. Animals with more developed cognitive capacities, such as NHPs, can be harmed more by involvement in research

¹² See the *Wet Dieren* (Animals Act), which came into effect in 2013.

¹³ Bentham, J., *An Introduction to the Principles of Morals and Legislation*.

¹⁴ Bovenkerk and Kaldewaij, 'The Use of Animal Models in Behavioural Neuroscience Research'. See also Robinson and Weiss, 'Primate Personality and Welfare'.

because, for example, they can experience boredom. Application of the principle of non-maleficence implies that we have a moral obligation to take account of the greater cognitive capacities of NHPs – both when considering the justification for their use in research and in relation to their wellbeing during research. Relational arguments are often advanced in this context as well. Such arguments may be based on the biological similarity of NHPs to humans, the degree of domestication and the extent to which we are able to relate to an animal. Arguments of that kind point to NHPs being afforded special status, because they are biologically closely related to humans and because we (subjectively) perceive NHPs to have human-like characteristics of appearance and behaviour that also make them socially more similar to humans.¹⁵

In light of such reasoning, an additional focus on NHPs is not arbitrary, but can be supported by morally relevant evidence that in practice justifies the refinement of generally applicable obligations in relation to matters such as the animal welfare implications of accommodation arrangements. Our particular moral obligations towards NHPs must be taken into account when considering the need for such animals to be used in research.

The importance of research

Judgements regarding animal experiments do not turn exclusively on an animal's right to protection. Scientific research is undertaken in pursuit of an objective that is deemed to be of value, such as the advancement of scientific knowledge or the promotion of human or animal health. The recognition that an objective has value does not automatically imply that it should be pursued by means of animal research, but it can be an important argument in support and defence of animal research. That is the case where all forms of animal research covered by the Wod are concerned. However, the special moral status of NHPs implies that more compelling evidence is needed to justify their use for research purposes than to justify the use of other animals. That principle is reflected in the Wod's requirement that the research should be concerned with debilitating or potentially life-threatening conditions (see section 1.5.2).

Weighing up values

On the basis of the considerations presented above, there is constant conflict in the obligations that apply in relation to animal experiments. For example, obligations concerning human health may conflict with obligations concerning animal welfare. Some people believe that the use of animals is never justified, while others approve of it for certain purposes. When asked whether it is acceptable to use laboratory animals, most of the experts we consulted said that it was, but stressed that their use should be subject to strict conditions. For example, some experts argue that some form of consent to participation should be expressed by animals before they may be used in research, just as with humans and for the same reasons. While questions arise as to how that principle might be applied in practice, it is founded on the belief that – even if an animal is unable to make an informed choice – we have an obligation to consider on the animal's behalf whether it would give its consent.

These differences in perception are not only the result of differences in personal views but also build on fundamentally different ethical-theoretical approaches. Consideration of the justification for experiments on NHPs is often based on a *utilitarian ethical framework*, where the emphasis is on maximising general well-being and minimising suffering.¹⁶ That involves assessing the ethical value of an action in terms of its consequences. In practice, however, that ethical framework is not usually

¹⁵ Arluke and Sanders, *Regarding animals*.

¹⁶ This framework is also the basis of the EU directive and therefore the Wod. The committee considers the other ethical frameworks as well in order to properly fulfil its task.

applied fully or consistently. Its application often differs from the theory, as introduced and refined by authors such as Peter Singer – an ethical harm-benefit analysis, in which the emphasis is on the avoidance of discomfort to animals.¹⁷

Ethicists and researchers active in the field of animal research increasingly argue that the utilitarian framework is inadequate for assessing the ethics of research involving NHPs. On the one hand, it is almost impossible to accurately predict the benefits of a study for all potential stakeholders; on the other hand, the harm caused to NHPs persists despite increasing efforts by ethics committees and the research community to minimise it.¹⁸

The utilitarian ethical framework also provides limited scope for assessing ethical considerations that are applied in science and society, but are difficult to translate in terms of happiness or well-being. Broader considerations not included in this utilitarian ethical framework include respect for animal integrity, animal dignity and the importance of human-animal relationships.¹⁹

Those considerations do play a role in other ethical frameworks such as *deontology*, which emphasises the quality of an action rather than its consequences. From this perspective, certain actions may be wrong in principle regardless of their consequences. The application of that ethical framework within animal ethics can imply an obligation not to treat animals as tools, even if doing so has no negative consequences for them, because such treatment would constitute a failure to recognise their intrinsic value. That line of reasoning is reflected in the Wod, for example in the bans on using great apes as laboratory animals and on using animals for testing cosmetics. Those activities are prohibited by the legislature even if the research in question could be done in a welfare-friendly way. Another viewpoint aligned with that school of ethical thought is that introduced by authors such as Tom Regan, who argues that all beings that possess a form of consciousness value their lives, regardless of whether others perceive that life to be of value.²⁰ By that criterion, an NHP's life is valuable in its own right and has inherent value, implying that NHPs should be afforded moral rights. One basic right is the right to never be treated exclusively as a tool for use in the realisation of another party's aims. From that perspective, research with NHPs is ethically indefensible, and only animal-free alternatives are justifiable.

Other arguments such as the importance of the human-animal relationship or consideration of animal dependency are central to a third ethical framework, *relational or care ethics*, which emphasises that unequal power relationships and dependency, including inequalities between humans and animals, are not a fact of life and should always be examined critically. It is necessary to consider whether they are just, whether they should be modified, and whether they imply any moral obligations. In practice, that approach involves first considering whether we have the moral right to use NHPs in research and thus to make them (more) dependent, leading to the establishment or continuation of a power imbalance. Even if it is concluded that we do have that right, it is necessary to consider whether, taking other relationships (e.g. with human patients) into account, we must exercise our right. Where our direct dealings with animals in a research context are concerned, that ethical framework implies that we have an obligation to treat the animals with care and consideration. Such care may vary from context to context, with the degree of dependence of the

¹⁷ Singer, *Animal Liberation*. Grimm, Olsson, and Sandøe, 'Harm-Benefit Analysis – What Is the Added Value?'

¹⁸ Carvalho et al., 'Ethical and Scientific Pitfalls Concerning Laboratory Research with Non-Human Primates, and Possible Solutions'.

¹⁹ Kramer, Bovenkerk, and ten Cate, 'Ontwikkelingen in de academische dierethiek en hun relevantie voor het denken over gebruik van dieren voor wetenschappelijk onderzoek' ['Developments in academic animal ethics and their relevance for thinking on the use of animals for scientific research']; Gruen and Fleury, 'Animal Welfare, Animal Rights, and a Sanctuary Ethos'.

²⁰ Regan, *The Case for Animal Rights*.

animal on humans being the determining factor. That may mean that the duty of care owed to NHPs in a research context differs from the duty of care owed to NHPs in the wild, since the latter are less dependent on human care.

The three ethical-theoretical frameworks mentioned above do not form an exhaustive expression of current schools of ethical thought, but make it clear that arguments concerning the justification for the scenarios for the future of NHP research cannot be considered in isolation from certain fundamental ethical principles. Although the various schools of ethical thought are associated with different visions and approaches, there is clearly a broad consensus that animals have moral value and that we can have direct obligations to animals, in the context of which NHPs have a special status because of their level of cognitive development and their biological and social similarity to humans.

Ethics as a central theme

On the basis of the analysis in this section, it is clear that research with NHPs and the debate about the future of such research are inseparable from ethical principles, obligations towards animals and humans, and ethical judgements. Ethics therefore form a central theme of this entire report. The reasons for considering the available alternative methods and the process of defining what constitutes a life-threatening condition are consequently informed partly by ethical arguments that imply that research must be thoroughly justified, and that alternatives must be sought. Nevertheless, it is important to emphasise that the committee does not see ethics as an established framework, on the basis of which one can directly deduce what is right and what is wrong. In light of the analysis presented above, it is understandable that there is still debate as to whether NHP research should continue and, if so, what conditions should apply. Political choices will need to be made regarding such matters, on the basis of considerations that are not exclusively ethical. Notwithstanding that reality, the committee will explicitly address ethics when outlining the various policy scenarios in part 2 of this report.

1.4 Protection of laboratory animals in general and NHPs in particular

1.4.1 The 3R (3V) approach and its limitations

The use of laboratory animals in scientific research is a matter of great ethical, scientific and social debate around the world. Laboratory animals such as mice, rats, rabbits and zebrafish are frequently used in scientific research to understand biological processes, disease mechanisms and the safety and effectiveness of new treatments.

In the Netherlands, the use of laboratory animals is subject to increasing regulatory control to assure the welfare of laboratory animals as far as possible. Such controls are often based on European or other international agreements. Several bodies are involved in providing advice, licensing and supervision. [Appendix 4](#) of this report details the historical context of the regulation of laboratory animal research in general and of NHPs in particular. In section 1.5, the committee examines the legal frameworks and the organisations involved in them.

In most countries, the so-called three Rs (in Dutch: 3Vs) are central to the ethical review procedures required by law to justify animal research. The principles in question were first proposed in 1959²¹:

²¹ Russell and Burch, *The principles of humane experimental technique*.

- *Replacement (Dutch: Vervanging)*: Replacing animal research with alternative methods, such as computer modelling, cell culture and other in vitro techniques. Animal research is allowed only when alternative models are not possible without greatly compromising the scientific value of the research.
- *Reduction (Dutch: Vermindering)*: Reducing the number of animals needed for research by using advanced statistical methods and study designs. The number of animals used should be limited as far as possible, providing that sufficient statistical power is retained.
- *Refinement (Dutch: Verfijning)*: Improving living conditions and methods to minimise animal suffering, such as better accommodation, anaesthesia, pain control and post-operative care; and improvement of the design of experiments, such as minimising stressful procedures and defining humane endpoints (see later in this report).²²

The systematics of Dutch legislation and the underlying European Union (EU) directive are also based on the three Rs.

There are also limitations to the 3R approach as a means of reducing the use of laboratory animals and promoting alternatives. The three Rs are applied on a case-by-case basis and their application therefore has limited impact in terms of the structural reduction of laboratory animal use in science. That was one of the reasons why the NCad published the report 'Transition to Animal-Free Research' in 2016, which proposed 'target images' or 'roadmaps' for phasing out basic and translational animal research in the Netherlands.²³ The ultimate objective was to make the Netherlands a global leader in animal-free research. The report proposed the development of a roadmap for each research area, aimed at phasing out the use of laboratory animals within that area. In response to the report, the TPI Programme was set up. In 2024, 124.5 million euros was invested in a national Centre for Animal-Free Biomedical Translation (CABT), proposed by the Ministry of LNVN (formerly LNV) and implemented by a core consortium of Utrecht University, UMC Utrecht, University of Applied Sciences Utrecht and RIVM. In 2024, the NCad published an evaluation of the transition approach. The evaluation concluded that the approach is useful, but that the current roadmaps do not adequately account for the perspectives of civil society groups outside the scientific community.²⁴

1.4.2 The special position of NHPs

In 2022, the Netherlands Food and Consumer Product Safety Authority (NVWA) recorded a total of 492,380 animal experiments in the Netherlands; 91 of those were carried out on NHPs, i.e. less than 0.02% of the total number of animal experiments.²⁵ Since the committee's investigation focuses exclusively on NHPs, it concerns only a small proportion of all research with laboratory animals carried out in the Netherlands and abroad.

However, societal concern about research on NHPs is understandable because of the animals' emotional and symbolic value. NHPs are cognitively and socially much like humans; they appear to

²² Buchanan-Smith et al., 'Harmonising the Definition of Refinement'.

²³ NCad, 'Transitie naar proefdiervrij onderzoek – Over mogelijkheden voor het uitfaseren van dierproeven en het stimuleren van proefdiervrije innovatie' ['Transition to animal-free research – About the scope for phasing out animal research and promoting animal-free innovation'].

²⁴ NCad, 'Evaluatie van het NCad advies "Transitie naar proefdiervrij onderzoek"' ['Evaluation of the NCad report "Transition to animal-free research"']. In its 2016 advice, the NCad proposed the Dutch concept 'streefbeeld', then translated in English as 'target image'. In 2024, the English word 'roadmap' was used for 'streefbeeld', to better align with EU terminology. The committee will henceforth use the term 'roadmap'.

²⁵ NVWA, 'Zo doende 2022: Jaaroverzicht dierproeven en proefdieren van de Nederlandse Voedsel- en Warenautoriteit' ['Doing it that way 2022: Netherlands Food and Consumer Product Safety Authority annual report on animal research and laboratory animals']. An animal experiment is the use of a single animal for a scientific purpose; projects and experiments typically involve multiple animal experiments. It is possible to use an individual animal more than once for an animal experiment. As a result, the actual number of animals used is lower than the number of animal experiments conducted.

value autonomy, and they undertake forward-looking projects. In public debate, therefore, they are often afforded a different status from other laboratory animals. As explained in section 1.3, there are also sound ethical grounds for according special status to NHPs in the context of animal research policy. The following section describes how that has led to specific regulations.

Because NHPs are genetically and physiologically more closely related to humans than other laboratory animals are, NHPs remain an important model in certain fields of research into human diseases. It is worth noting that, despite NHPs' similarity to humans, NHP models do not necessarily yield the best research results. Moreover, the close relationship between NHPs and humans is the basis for much of the criticism of the use of NHPs in scientific research.

The special position of NHPs is also translated into Dutch law. All animal experiments require prior approval, but the Wod stipulates that experiments on NHPs must meet stricter conditions than experiments on animals of other species. Moreover, unlike other animal research, research projects involving NHPs are assessed retrospectively as an additional safeguard. There are also additional requirements regarding breeding and registration. That topic is considered in more detail in the next section.

1.5 Laws and regulations on keeping NHPs and carrying out NHP experiments

1.5.1 European Union (Animal Experiments Directive)

Laws and regulations are harmonised within the EU, so that legal conditions are similar in all EU member states. Regulations are not harmonised with countries outside the EU, and there are no international treaties governing experiments with NHPs outside the EU. Many countries do, however, have national laws and ethical guidelines regulating the use of animals in research.

In the European Union, animal research is regulated by Directive 2010/63/EU on the Protection of Animals Used for Scientific Purposes, more commonly known as the Animal Experiments Directive. The directive makes strict requirements regarding the ethical review of and justification for animal experiments, the care of animals, and the promotion of alternative methods to reduce the use of animals. Its aim is to ensure animal welfare while also promoting scientific progress. The directive includes several articles relating specifically to NHPs.²⁶

This directive came into force in 2010. Member states are bound by it, but a directive, unlike a regulation, does not have direct effect: member states must first implement it in national laws and regulations. Such implementation may result in differences between countries. When implementing a directive, member states are allowed to define exceptions allowing certain national rules that predate and are stricter than the EU directive to remain in force. In the Netherlands, for example, stricter rules on registration, accommodation, care provision and the age at which mothers and young may be separated have traditionally applied to NHPs. Since the directive's implementation in Dutch national legislation and regulations in 2014, it has not been possible to introduce any new animal research policies that are stricter than the EU directive, so that a level playing field remains across Europe.

²⁶ European Parliament and Council, 'Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the Protection of Animals Used for Scientific Purposes'. See also SCHEER, *Final Opinion on the Need for Non-Human Primates in Biomedical Research, Production and Testing of Products and Devices (Update 2017)*.

From its interviews with researchers, the committee understands that, in the Netherlands, possible research projects are assessed very carefully before consent is given for the use of NHPs, while shorter procedures are followed in some other European countries.

The EU directive specifies four legal types of research with NHPs.²⁷

1. Basic research
2. Translational or applied research
3. Regulatory use and routine production research
4. Research aimed at preservation of the species

Information from the ALURES database indicates that, in the EU, most NHP research is regulatory (category 3) research. In the Netherlands, however, the situation is different: here, most NHP research is basic or translational research (category 1 or 2). In this report, therefore, the committee focuses mainly on the latter two types of scientific research with NHPs. Dutch pharmaceutical companies will inevitably commission regulatory NHP research as well – most of it performed in other countries – but such research is outside the committee's remit.

European regulation of medicines (registration, safety testing) is discussed further in 1.5.4.

1.5.2 Dutch laws and regulations (Animal Experiments Act)

Since 2014, the Netherlands has implemented the European Animal Experiments Directive 2010/63/EU into national law and regulations by revising the Wod. The Animal Experiments Directive and the Wod are based on the principle that *no* animal experiment should be carried out *unless*:

- there are compelling reasons for the research, and
- no suitable alternative methods exist (Section 1 of the Wod), and
- the research is performed by a *licensed institution* (Sections 2, 3, 4, 6, 7 and 8), and
- the research is performed by suitable authorised and competent personnel (Sections 9 and 13f2).

Research with NHPs is covered by additional requirements. Under the Wod, NHP research is in principle forbidden, unless²⁸:

- Scientific evidence can be presented demonstrating that the purpose of the animal experiment cannot be achieved by the use of other animals, **and**;
- The research is applied research aimed at the reduction, prevention, diagnosis or treatment of debilitating or potentially life-threatening clinical conditions in humans; **or**;
- The research is basic research or research aimed at preservation of the species of NHP in question.

The Wod thus attaches broader conditions to the permissibility of NHP research than those set out in the committee's task definition, which refer to the use of NHPs being permissible for research into 'infectious diseases that threaten public health' and 'life-threatening diseases'. The Committee will return to this distinction in the next chapter.

The national implementation of the European Animal Experiments Directive 2010/63/EU took account of the fact that critical debate on the (un)desirability of animal research had been ongoing in the Netherlands for many years. For some, the Wod was a logical and appropriate extension of what was already happening; for others, the national implementation did not go far enough in reducing animal research.

²⁷ The four types in question are deduced by reading articles 5 and 8 of Directive 2010/63/EU in conjunction.

²⁸ Wet op de Dierproeven (Wod, Animal Experiments Act). Section 10e, subsection 2 and Section 1c

The national implementation of 2010/63/EU was given two main pillars in 2014. Two licences are required to conduct an animal experiment:

1. *An institutional licence* This is requested by the research institution or company from the Dutch Food and Consumer Product Safety Authority (NVWA). Under the Wod, institutions must meet various requirements to qualify for a licence. For example, an institution must set up an Animal Welfare Body (*IvD = Instantie voor Dierenwelzijn*), which is responsible for the internal supervision of animal welfare and must include at least one researcher. In addition, both the researchers and animal handlers involved must be licensed to work with the laboratory animals, and must possess appropriate specific authority and competence. The NVWA supervises institutional licence holders through inspection visits, both announced and unannounced. The number of animal experiments performed by each licence holder each calendar year is reported to the NVWA.²⁹
2. *A project licence* Prior to conducting any animal experiment, researchers affiliated to a licensed institution must apply for a project licence from the Central Committee on Animal Experiments (CCD). Before applying for a project licence, the researchers must contact the Animal Welfare Body (*IvD*) within the institution. If approved by the *IvD*, the project proposal proceeds to the CCD. The CCD establishes whether the benefit of and need for the animal experiment outweighs the discomfort to the animals, and whether there are no alternative methods available or methods that are less harmful to the animals. The number of laboratory animals is also considered: the aim is to use as few animals as possible, while also ensuring that the study and results are sufficiently reliable and relevant for the study to have statistical significance. The Animal Experiments Committee (DEC) plays an important advisory role in this process (see also below). Like the CCD, the DEC consists of experts in animal ethics, animal health, alternative scientific methods and other research. The DEC assesses whether the experiment meets legal and ethical requirements, and then advises the CCD whether the experiment should or should not be licensed. The DEC's advice is important to the CCD's decision-making process. A project licence, valid for up to five years, will be issued only if the CCD considers and expects that the importance of the research will outweigh the discomfort experienced by the animals. Before the researcher can start the experiment, a detailed working protocol must also be submitted to the *IvD*. The protocol must include the number of animals needed, an estimate of the discomfort the animals are liable to experience, and a description of the circumstances under which active steps will be taken to end or reduce their suffering by means of euthanasia or by ending the experiment.³⁰ At the end of the experiment, the actual suffering is determined and recorded. During long-term experiments, suffering is monitored by institutional animal handlers.

To further reinforce the review and supervision of animal research, several authorities and advisory bodies have been created:

- The NVWA, as regulator, grants institutional licences for animal research, and checks whether institutions work according to the rules.³¹
- Internal Animal Welfare Bodies (*IvDs*) supervise how animal research is conducted, paying specific attention to animal welfare and adherence to the three Rs within the institution. Every institution licensed to conduct animal research is required to establish an *IvD*.

²⁹ NVWA, 'Zo doende 2022: Jaaroverzicht dierproeven en proefdieren van de Nederlandse Voedsel- en Warenautoriteit' ['Doing it that way 2022: Netherlands Food and Consumer Product Safety Authority annual report on animal research and laboratory animals].

³⁰ *IvD* Utrecht, 'Humane eindpunten' ['Humane endpoints'].

³¹ NVWA, 'Dierproeven voor onderzoek' ['Animal experiments for scientific research'].

- The CCD is the authority responsible for licensing animal research in the Netherlands. The CCD reviews project applications on ethical and scientific grounds. The CCD is an independent administrative body under the Ministry of LNVN (formerly LNV).
- DECAs are often, but not necessarily, allied to research institutions, and they give advice to the CCD regarding licence applications. Their main task is the ethical review of animal research applications. That includes assessing whether the importance of a project outweighs the discomfort to the animals involved: a so-called harm-benefit analysis. The DEC then advises the CCD whether the benefit does or does not outweigh the harm.³²
- There is also the NCad, an advisory body under the Ministry of LNVN (formerly LNV), which provides solicited and unsolicited advice to the Minister of LNVN (formerly LNV), the CCD and IvDs on the acquisition, breeding, accommodation, care and use of animals in experiments. The underlying objective of the NCad's role is the replacement, reduction and refinement of animal research.³³

The application procedure for NHP research is the same as for other forms of animal research, as described above. The Wod additionally requires that, in any NHP study involving severe discomfort for the animals, special conditions regarding so-called 'retrospective assessment' must be met. In the retrospective assessment, researchers provide information on³⁴:

- whether the project's goals were achieved;
- what degree of discomfort the animals experienced;
- how many laboratory animals were used;
- what types of laboratory animal were used;
- what applications can contribute to further progress towards the required replacement, reduction and refinement in practice.

The committee notes that criticism of the existing arrangements for the ethical review of animal research has been expressed; the suggestion being that it should be stricter. Specifically, there is no requirement that the assessment of a licence application should include either systematic consideration of the application of the three Rs or a systematic literature review to support the decision to adopt an animal model for the research.

In animal research, and particularly in experiments involving NHPs, transparency regarding the research practices is considered especially important. For example, the NVWA and the CCD publish annual reports to provide insight into the trends, numbers and types of animal experiments carried out in the Netherlands. An important step in promoting transparency was the introduction of the Non-Technical Summary (NTS). The NTS is part of the project licence application for animal research and aims to inform the public about the nature and purpose of the research. The summaries are published on the website of the European Commission in the ALURES database.³⁵

1.5.3 Animal discomfort

The DECAs and CCD assess applications for project licences by means of a so-called harm-benefit analysis. Such an analysis involves weighing up the potential benefits of the research against the

³² CCD, 'Centrale Commissie Dierproeven' ['Central Committee on Animal Experiments'], <https://www.centralecommissiedierproeven.nl/>

³³ NCad, 'Nationaal Comité advies dierproevenbeleid' ['National Advisory Committee on Animal Research Policy'], <https://www.ncadierproevenbeleid.nl>

³⁴ CCD, 'Aanvraagformulier projectvergunning' ['Project licence application form'].

³⁵ European Commission, 'ALURES'. Until 2021 on the website of the CCD, 'Onderzoekssamenvatting (NTS)' ['Non-technical summary'].

discomfort that the animals are expected to experience during the research.³⁶ In that context, 'discomfort' means any detriment to an animal's welfare, such as pain, suffering, anxiety, or temporary or permanent harm. For a scientific research project to be deemed ethically responsible, the researchers must be aware of the discomfort animals are liable to experience, and must endeavour to minimise it. A harm-benefit analysis is not a straightforward procedure based on a simple mathematical equation. For example, the CCD must consider whether it is better to inflict less discomfort on a larger number of animals, or more discomfort on a smaller number of animals.³⁷

The degree of discomfort also determines whether a study falls under the definition of an animal experiment under the law. A study qualifies as an animal experiment if the animal experiences as much or more pain, suffering, anxiety or lasting harm as when a needle is inserted in accordance with good veterinary practice.³⁸ That applies in relation to all animals that have the capacity to experience pain, including unborn and unhatched animals in the final phase of the gestation period and genetically modified animals whose generation or breeding is associated with discomfort.³⁹ Killing animals to use their organs, tissues or body fluids also falls within the scope of the Wod.⁴⁰

Examples of discomfort in animal research include:

- Physical discomfort: ranging from temporary discomfort such as drawing blood, to persistent pain due to surgical procedures or repeated exposure to substances.
- Stress and anxiety: arising from handling, isolation, transport or exposure to unfamiliar environments.
- Restricted movement: in cages or containers if the spaces in question are not in keeping with the animals' natural behavioural needs.
- Social discomfort: in social animals separated from congeners or when their social interactions are restricted.

To minimise discomfort, certain measures must be taken, such as:

- Good accommodation conditions: ensuring adequate space, climate control and hygiene.
- Environmental enrichment: offering social interaction, physical and cognitive enrichment, such as climbing frames and toys.
- Pain management and anaesthesia: use of analgesics and anaesthetics to minimise pain before, during and after procedures.
- Good training protocols: following guidelines to reduce stress and anxiety.
- Regular monitoring: recognising early signs of stress, pain, or discomfort and making adjustment(s).
- Refinement of experiments: using the least invasive techniques and limiting the duration of procedures.

To estimate the degree of discomfort, the EU regulation distinguishes different categories⁴¹:

- Light: a short period of mild pain, anxiety or suffering (e.g. an injection or a short period of hunger).

³⁶ NCad, 'Inschatten van Cumulatief Ongerief' ['Estimation of Cumulative Discomfort']. NCad, 'Zienschwizje: Afwegingskader voor het Prioriteren van Dierproeven voor Vervanging'.

³⁷ NCad, 'Verslag digitale bijeenkomst CCD/NCad 28-09-2020' ['Report on virtual CCD/NCad meeting 28-09-2020'].

³⁸ CCD, 'Wetten en regels' ['Laws and rules'].

³⁹ CCD, 'Herziene handreiking "Het genereren, fokken, genotyperen, monitoren en houden van genetisch gewijzigde dieren"' ['Revised guidelines "The generation, breeding, genotyping, monitoring and keeping of genetically modified animals"'].

⁴⁰ Breeding animals for scientific research (as laboratory animals) also falls under the protection of the Wod.

⁴¹ Wet op de Dierproeven (Wod, Animal Experiments Act).

- Moderate: prolonged mild pain or short-term moderate pain (e.g. chemotherapy or recovery from surgery).
- Severe: prolonged moderate pain or severe pain (e.g. prolonged infection studies in monkeys with severe disease).
- Terminal: animals are placed under general anaesthetic and subsequently killed.

Several factors need considering in order to categorise the degree of discomfort: the type of laboratory animal, its natural behaviour or habitat and the impact of the procedure. Cumulative discomfort (the sum total of multiple forms of discomfort) is also included in the assessment; this can lead to the discomfort being placed in a higher overall category.⁴²

An animal may also be killed or removed from an experiment to prevent it from experiencing more discomfort than the maximum estimated. This is referred to as the 'humane endpoint'. When submitting an application for a project licence, the applicant indicates whether there are circumstances where humane endpoints would need to be applied to prevent further suffering for the animals. The project licence application forms identify three reasons for terminating an experiment prematurely (humane endpoints):

1. An animal's discomfort exceeds the permissible upper limit described in the project plan.
2. The scientific endpoint of the experiment has been reached (e.g. a predetermined tumour size).
3. The scientific endpoint can no longer be reached (e.g. due to disturbance of symptoms in the animal).⁴³

In cases where a humane endpoint is reached, the animal may be killed, or the experiment may be modified to reduce discomfort without killing the animal. If death is used as an endpoint, the project licence application must explain why humane endpoints are not possible, and must specify the measures to be taken to minimise adverse effects.

1.5.4 Industry and medicine regulation

The European Union has regulated the development of medicines and clinical research into the working of medicines.⁴⁴ In the Netherlands, the relevant EU legislation is implemented by means of the Medicines Act and the Medical Research (Human Subjects) Act.⁴⁵ Those acts form the legal background to the debate regarding animal research and NHPs.

NHPs play an important role in medicine development and regulation – not so much because large numbers of NHPs are used but because they are currently considered indispensable at some critical junctures in the process of developing medicines (a view that is not universally accepted, as the committee will explain in this report). For many years, NHP experiments have been part of the standard research repertoire used by medicine developers, especially in 'safety pharmacology' – research that focuses on the safety of drugs in the short term and long term (e.g. repeat dose toxicology) and in certain high-risk groups (e.g. reprotoxicity). That is especially true in relation to

⁴² NCad, 'Inschatten van Cumulatief Ongeriep' ['Estimation of Cumulative Discomfort'].

⁴³ CCD, 'Aanvraagformulier projectvergunning' ['Project licence application form'].

⁴⁴ European Commission, Regulation (EC) No. 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Union procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. European Commission, Regulation (EU) No. 536/2014 of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC.

⁴⁵ Medicines Act; Medical Research (Human Subjects) Act.

biologics (e.g. monoclonal antibodies⁴⁶), vaccines and gene therapies. In the Netherlands, such experiments are carried out by the BPRC, but companies in the Netherlands also use NHP facilities abroad, including in China. (NHPs also continue to play a role in the research into the safety of medicines and medical materials that is required by law. However, such research is not carried out in the Netherlands; see also section 1.5.1 of this report. The BPRC does not carry out regulatory research with NHPs into the toxicology of chemicals, vaccines or medicines; as far as the committee can establish, such research is not carried out elsewhere in the Netherlands either.) The pharmaceutical industry does sometimes carry out such research, because it interprets the various international regulatory guidelines (e.g. as published by the European Medicines Agency (EMA), the US Food and Drug Administration (FDA), or Japan's Pharmaceutical and Medical Devices Agency (PMDA)) as requiring the use of NHPs. The industry believes that departing from that interpretation could jeopardise the approval of its products.⁴⁷ In principle, the industry could use scientifically evidenced alternatives to NHPs, but the acceptance of such alternatives by the regulatory authorities requires the investment of time and energy on both sides, without any certainty regarding the outcome.

At the same time, there has long been a global debate about the need for and added value of NHPs in medicine development and regulation. The 3R principles are widely supported. The industry and the registration authorities also cooperate in European and other consortia with the aim of reducing the use of NHPs. Discussion regarding the reduction of NHP use has intensified since the SARS-CoV-2 pandemic. During the pandemic, a global shortage of NHPs arose, driven by increasing demand for NHPs for use in vaccine development (including use in the Netherlands at the BPRC), coupled with reduced supply, due to China halting its export of NHPs. As a result, the cost of NHP research rose sharply.⁴⁸

Within both the industry and the registration authorities, those factors created a sense that the search for alternatives to NHP use should be urgently accelerated, with a view not only to reducing the number of NHPs required, but also to increasing the effectiveness of research. That view was informed partly by the fact that the shortage of NHPs was leading to suboptimal use of the animals (e.g. for small studies with fairly low statistical power), and was acting as a brake on the replication of experiments. In 2022, the FDA went as far as discouraging the use of NHP experiments for the development of SARS-CoV-2 vaccines and conditionally permitting the use of experiments on other animals.⁴⁹ That measure was facilitated by the fact that a number of SARS-CoV-2 vaccines made use of familiar vaccine platforms (e.g. for Ebola), for which a great deal of safety data was already available.⁵⁰ After the pandemic, however, the FDA withdrew its relaxation of the rules.⁵¹

From a distance, it appears that the industry and the regulatory authorities are holding each other back.⁵² The development of medicines is important to the world. A world where established procedures and dominant actors are extremely influential. Although the Netherlands' direct

⁴⁶ See, for example: Brennan et al., 'Safety testing of monoclonal antibodies in non-human primates'.

⁴⁷ For an overview of international regulations, see Bayne, Hau, and Morris, 'The Welfare Impact of Regulations, Policies, Guidelines, and Directives and Nonhuman Primate Welfare'.

⁴⁸ Brown and Wange, 'Considerations Regarding the Use of Nonhuman Primates in Assessing Safety Endpoints for Pharmaceuticals'.

⁴⁹ FDA, 'Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints Arising From the COVID-19 Pandemic; Guidance for Industry; Availability'.

⁵⁰ See also section 2.1.1 of this report.

⁵¹ Brown and Wange, 'Considerations Regarding the Use of Nonhuman Primates in Assessing Safety Endpoints for Pharmaceuticals'.

⁵² Harrell et al., 'Endeavours Made by Trade Associations, Pharmaceutical Companies and Regulators in the Replacement, Reduction and Refinement of Animal Experimentation in Safety Testing of Pharmaceuticals'.

involvement in the field is limited, the Dutch Medicines Evaluation Board (CBG) has been encouraging research into the usefulness of and necessity for using NHPs for many years.⁵³ Collaboration with academic researchers, with registration authorities elsewhere in Europe and beyond, and with the industry is yielding answers to questions regarding the translational value of NHP research, regarding the strength of the evidence actually required to contribute to increased medicine safety, and regarding the necessity of using NHPs in that context. The CBG also continually reflects on the question of what criteria (context of use, fitness for purpose) NAMs should meet to be considered internationally acceptable by the International Council for Harmonisation (ICH), EMA, FDA, or PMDA.⁵⁴ Such initiatives are increasingly embraced and supported by funding from sources in the Netherlands and elsewhere.⁵⁵ From the expert interviews it conducted, the committee understands that there is growing criticism of NHP experiments from the authorities that regulate clinical research, such as the EMA in Europe and the Central Committee on Research Involving Human Subjects (CCMO) in the Netherlands. Whether the use of NHPs adds scientific value depends very much on the nature of the product under development. If the mechanism of action, or pharmacology, is well understood, there is little need for NHP experiments, according to the experts interviewed by the committee.

Despite all efforts to develop NAMs and review the regulations regarding safety testing of medicines and medical devices, a common theme of the input received from both the industry and the authorities is that, although a great deal is happening, the field is still very fragmented, and that research is not adequately focused on achieving substantial change in the foreseeable future.⁵⁶ Although there is broad consensus that change is needed, within the regulatory system there is still conviction that NHPs are indispensable, especially for biologics, vaccines and gene therapy.⁵⁷ The expected growth in the development of such products in the coming years is liable to actually increase the demand for NHPs. There are calls on both sides for further dialogue and alignment (regulatory harmonisation) to develop NAMs more quickly and increase acceptance. Through the CBG in particular, the Netherlands acts as an important catalyst for such development. NHP experiments are also on the EMA agenda.⁵⁸ ICH is seen as an important platform for achieving the necessary global impact.⁵⁹

⁵³ Meer et al., 'The Ability of Animal Studies to Detect Serious Post Marketing Adverse Events Is Limited'.

⁵⁴ See, for example: Meer et al., 'The Value of Non-Human Primates in the Development of Monoclonal Antibodies'. Prior et al., 'Exploring Greater Flexibility for Chronic Toxicity Study Designs to Support Human Safety Assessment While Balancing 3Rs Considerations'.

⁵⁵ ZonMw, 'Meer kennis met minder dieren: stuwende kracht in de transitie naar proefdiervrije innovaties' ['More knowledge with fewer animals: driving force in the transition to animal-free innovation'].

⁵⁶ Many activities are also being undertaken by the (pharmaceutical) industry to reduce the use of laboratory animals and NHPs. For example, see the website of the European Federation of Pharmaceutical Industries and Associations: EFPIA, 'Putting Animal Welfare Principles and 3Rs into Action - European Pharmaceutical Industry Report - 2022 Update'.

⁵⁷ It is therefore important that licensing authorities ask for strong evidence that a proposed NHP research project is indeed necessary, such as evidence from systematic reviews: Sievers, Wieschowski and Strech, 'Investigator Brochures for Phase I/II Trials Lack Information on the Robustness of Preclinical Safety Studies'. Wieschowski et al., 'Preclinical Efficacy Studies in Investigator Brochures'.

⁵⁸ Within the EMA, a drafting group is studying possible alternatives to NHP experiments. The results of the work are likely to be published in the course of 2025.

⁵⁹ See, for example: ICH, 'S11 Nonclinical safety testing in support of development of pediatric pharmaceuticals - Guidance for Industry'.

2 Application of NHP experiments

2.1 Scientific relevance

The committee was tasked with investigating whether it is possible to further reduce the number of experiments performed using non-human primates, without compromising research that is strictly necessary for controlling life-threatening diseases and outbreaks of infectious diseases that threaten public health.

In this chapter, the committee considers the importance of NHP models for research into such diseases. That requires the phrases ‘infectious diseases that threaten public health’ and ‘life-threatening diseases’ to be carefully defined at the outset, because they are used in the committee’s assignment, but *not* in the Wod. As explained in the previous chapter, the law is currently based on a broader definition of diseases for which NHP experiments are in principle allowed. The Wod states that NHPs may not be used as laboratory animals unless the research in question contributes to the avoidance, prevention, diagnosis or treatment of debilitating or potentially life-threatening clinical conditions in humans, and no alternative research methods are available. The scope of that definition extends beyond pandemic and life-threatening diseases. In the remainder of this report, the committee therefore makes no further use of the broad term ‘debilitating conditions’, but explores the scope for using ‘infectious diseases that threaten public health’ and ‘life-threatening diseases’ as criteria. It is desirable to investigate those stricter criteria for permitting NHP research, because they could be implemented without any conflict with the Wod or the underlying EU Animal Experiments Directive, by attaching conditions to the funding of the BPRC.

2.1.1 Infectious diseases that threaten public health and the importance of NHP research

An ‘infectious disease that threatens public health’ can be defined as a disease caused by micro-organisms, such as bacteria, viruses, parasites or fungi, which poses a significant risk to the health of many people in a specific population or geographical region. Such diseases can generally spread rapidly and can lead to serious health problems and possibly death. In the Netherlands, RIVM’s Centre for Infectious Disease Control (Cib) coordinates the control of infectious diseases.⁶⁰

The characteristics of an infectious disease that threatens public health are⁶¹:

- *High infectivity*: The disease can be easily transmitted from human to human, animal to animal, animal to human and *vice versa*, allowing rapid spread.
- *Potential for serious consequences*: The disease can lead to serious health complications, including hospitalisation, permanent harm or death.
- *Limited or no immunity in the population*: People have little or no immunity to the causative pathogen, which can contribute to the rapid spread of infection.
- *Social disruption*: The disease can lead to disruption of normal social activities, including healthcare systems, economies and daily life. The cause does not necessarily have to be natural: disruption caused by infectious disease can also be intentionally instigated by a hostile actor.⁶²

⁶⁰ RIVM, ‘Infectieziektenbestrijding’ [‘Infectious disease control’].

⁶¹ Analistennetwerk Nationale Veiligheid, ‘Themarapportage infectieziekten’ [‘Themed report on infectious diseases’]. Giessen, Giessen and Braks, ‘Emerging zoonoses: Early warning and surveillance in the Netherlands’.

⁶² EMA, ‘EMA Guidance Document on the Use of Medicinal Products for Treatment and Prophylaxis in Case of Exposure to Biological Agents Used as Weapons of Terrorism, Crime or Warfare’.

Examples of infectious diseases that can threaten public health are pandemic flu and severe outbreaks of other viral infections such as SARS-CoV-2 and Ebola, endemic diseases such as measles, polio, RSV (respiratory syncytial virus), malaria, dengue, and emerging infections such as Zika, WNV (West Nile virus), and mpox. Controlling such infectious diseases requires rapid response, international cooperation and effective public health measures. As a result of factors such as the increase in global human mobility, human encroachment on animal habitats, and climate change, new infectious diseases that are currently unknown may emerge, and infectious diseases may spread to areas where they were not previously present.

In scientific research on infectious diseases, NHPs are uniquely valuable because their immune systems are the most closely related to the human immune system, meaning that they are considered the most suitable animals for vaccine and medicine testing.⁶³ NHP research is conducted in the preclinical phase of vaccine development, when the safety and efficacy of candidate vaccines is investigated before the vaccines are tested on humans. Such investigation is required by the EMA and CBG, so that potential side-effects may be identified and the optimum dosages established.⁶⁴ Furthermore, infectious disease research is concerned not only with vaccine development, but also with study of the disease itself (pathogenesis studies) and of potential treatments. An infectious disease is often a multi-organ problem (affecting the respiratory tract, brain, gastrointestinal tract, in combination with the immune system). Due to the limited 'host range' of pathogens, such problems can sometimes be studied only in species that are closely related to humans. However, it should also be noted that there are significant differences between NHPs and humans, which may limit the translational value of NHP research.⁶⁵

In the Netherlands, the BPRC studies infectious diseases such as malaria, HIV, tuberculosis and emerging infectious diseases, as well as autoimmune diseases such as rheumatoid arthritis and multiple sclerosis, and the prevention of rejection in organ transplantation. The international review of scientific publications commissioned by the committee found that the Netherlands plays an important role in NHP research into tuberculosis: since 2019, there has been Dutch involvement in 14 per cent of global tuberculosis research undertaken using NHPs. [Figure 1](#) lists the diseases into which NHP research has been conducted since 2019. All the articles in question relate to new medicines and vaccines, but some also relate to research into the underlying fundamental processes.⁶⁶

Analysis of the international literature on NHP research in the period 2020 to 2024 shows that SARS-CoV-2 dominated academic research using NHPs in those years ([Figure 1](#)).⁶⁷ The publication counts show that the number of NHP studies carried out worldwide has been stable for the last six years, but that there was a significant spike during the SARS-CoV-2 pandemic because NHPs, like humans but unlike mice, are susceptible to SARS-CoV-2. The licensing of NHP research for vaccine development was accelerated by the CCD. In a period of just one year, multiple vaccines against this infectious disease were developed and approved by EMA. That was achieved by quickly establishing

⁶³ See, for example, De Swart, 'Measles'. Estes, Wong and Brenchley, 'Nonhuman Primate Models of Human Viral Infections'.

⁶⁴ EMA, 'Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-Clinical and Clinical Issues'.

⁶⁵ Ferreira et al., 'Translatability of Preclinical to Early Clinical Tolerable and Pharmacologically Active Dose Ranges for Central Nervous System Active Drugs'. NCad, 'Streefbeeld voor proefdiervrije innovaties in de immunologie' ['Road map for animal-free innovation in immunology'].

⁶⁶ KNAW, 'Gebruik van niet-humane primaten (NHP) als proefdier. Nut of Noodzaak?' ['Use of Non-Human Primates (NHPs) as Laboratory Animals. Convenience of Necessity?']

⁶⁷ See also: Albrecht et al., 'COVID-19 Research'. Genzel et al., 'How the COVID-19 Pandemic Highlights the Necessity of Animal Research'. However, see also: Ritskes-Hoitinga, 'Medical Regulators'.

numerous international collaborative projects involving research groups with expertise in different fields. The BPRC, Erasmus MC, Leiden University Medical Centre and other Dutch universities were involved in the testing of various SARS-CoV-2 vaccines, contributing to international efforts to develop safe and effective vaccines against the disease.⁶⁸ The Dutch institutions made a very important contribution to the reduction of mortality and long-term disability, and to enabling the phase-out of measures introduced to control the spread of SARS-CoV-2.⁶⁹

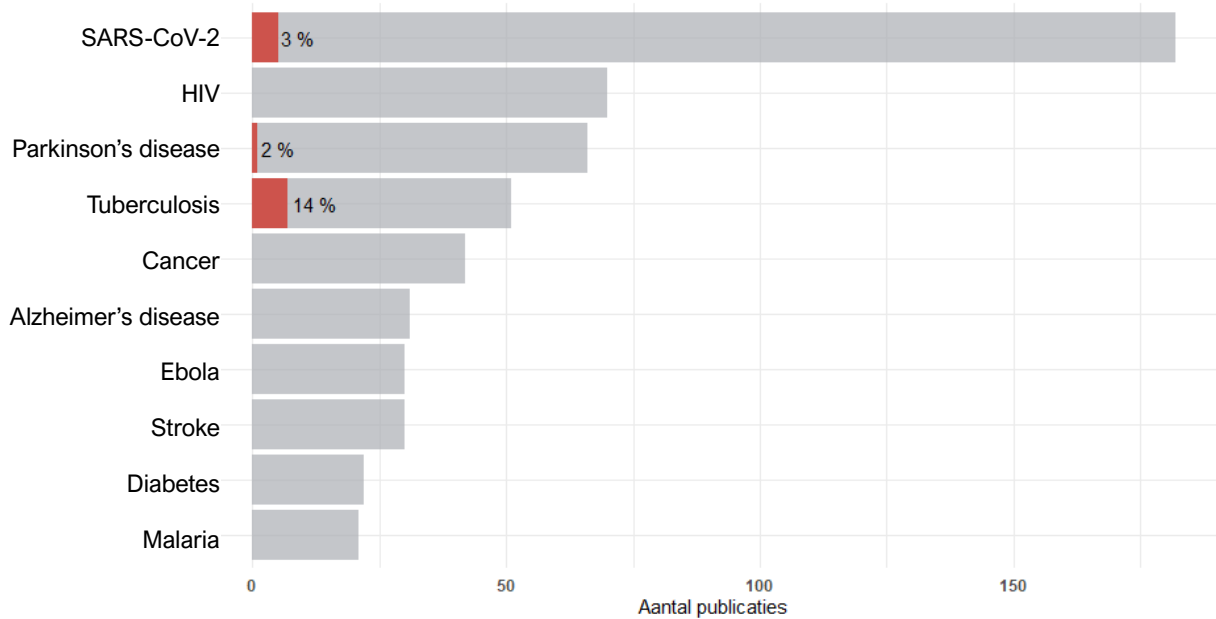


Figure 1 Overview of global (grey) and Dutch (red) NHP research by disease area from 2019 to 2024 (based on numbers of scientific publications).

Nevertheless, there is also some doubt within the scientific community as to whether it was actually necessary to use NHPs for the development of SARS-CoV-2 vaccines.⁷⁰ The importance of NHP research has been questioned in light of the fact that vaccines were already being tested in humans while the NHP studies were ongoing, rather than delayed until the NHP studies were concluded. In the development of the BioNTech/Pfizer and Moderna vaccines, there was considerable reliance on data from earlier human and NHP research into other vaccine platforms, such as the Ebola platform, on which a lot of safety data was already available.⁷¹ The relatively new mRNA vaccine technology has been the subject of scientific study since the 1990s, and the first mRNA vaccines for prostate cancer and MERS were licensed in 2013.⁷² Critics therefore argue that a 'weight-of-evidence' approach could

⁶⁸ Solforosi et al., 'Immunogenicity and Efficacy of One and Two Doses of Ad26.COVID.S COVID Vaccine in Adult and Aged NHP'. Rockx et al., 'Comparative pathogenesis of COVID-19, MERS, and SARS in a nonhuman primate model'. McDonald et al., 'Comparative Systematic Review and Meta-Analysis of Reactogenicity, Immunogenicity and Efficacy of Vaccines against SARS-CoV-2'.

⁶⁹ Koopman et al., 'Imaging the Immune Sequelae of Infection with SARS-CoV-2 in Nonhuman Primates by Using Two Nanobody PET-Tracers'. Nieuwland et al., 'Longitudinal Positron Emission Tomography and Postmortem Analysis Reveals Widespread Neuroinflammation in SARS-CoV-2 Infected Rhesus Macaques'. Philippens et al., 'Brain Inflammation and Intracellular α -Synuclein Aggregates in Macaques after SARS-CoV-2 Infection'.

⁷⁰ Ritskes-Hoitinga, Barella and Kleinhout-Vliek, 'The Promises of Speeding Up'.

⁷¹ Albrecht et al., 'COVID-19 Research'. Wolf et al., 'Applying Lessons from the Ebola Vaccine Experience for SARS-CoV-2 and Other Epidemic Pathogens'.

⁷² Casadevall, 'The mRNA Vaccine Revolution Is the Dividend from Decades of Basic Science Research'. Chaudhary, Weissman and Whitehead, 'mRNA Vaccines for Infectious Diseases'.

have been used to make the case that NHP experiments were no longer necessary for the development of SARS-CoV-2 vaccines.⁷³ The weight-of-evidence approach is a method of assessing the strength and reliability of scientific evidence by combining and weighing different sources of evidence. The EMA allows the method to be used in appropriate cases to argue that the pre-existing data and evidence are sufficient for the assessment of a medicine and that NHP experiments are therefore not necessary. That did happen to some extent during the pandemic, with major clinical studies in humans being approved at a relatively early stage (to be conducted in parallel to the NHP research). In addition, large-scale vaccine production was started before all the test results were available.⁷⁴

Nevertheless, NHPs did play an important role in the accelerated development of SARS-CoV-2 vaccines. For example, important NHP experiments were carried out for dose optimisation and boost strategy formulation, to investigate potential safety issues, such as the risk that T helper cells could cause a vaccine-associated aggravated respiratory tract disease, and to study ways of predicting effectiveness against various virus variants.⁷⁵ It is difficult to retrospectively assess how the development of vaccines would have progressed without NHP research. However, it is reasonable to assume that the process would have taken significantly longer and that a larger number of clinical trials involving more human subjects would have been necessary, increasing the safety and efficacy risks.

The scope for building on previous research in a future pandemic is uncertain: in a future pandemic involving a new strain of influenza, it is likely that few NHPs would be needed, but virologists believe that NHP research would be essential in a future pandemic involving an unknown virus or infectious disease.

Another important consideration is *what proportion of the world's population* is at risk from the infectious disease in question. At the moment, some infectious diseases (so-called 'poverty-related diseases') occur only in the 'global south', i.e. in low- and middle-income countries, and are not (yet) endemic in the Netherlands or other Western countries, where they occur only as imported diseases.⁷⁶ Nevertheless, with any infectious disease against which there is no effective vaccine or proper treatment, and/or which involves a pathogen that has developed resistance to multiple antibiotics, there is a possibility that the disease could also become endemic in the Netherlands due to factors such as high global mobility and climate change, or if used in the context of bioterrorism. For those and other reasons, research into such infectious diseases remains important for Dutch public health.

One element of the committee's assignment was to "look at strategic European autonomy and (reducing) dependence on other countries where, for example, vaccine development is concerned."⁷⁷ The issue of strategic autonomy is relevant to various scientific fields, but is significant for NHP research mainly where the control of pandemic infectious diseases and the development of vaccines

⁷³ Ritskes-Hoitinga, Barella and Kleinhout-Vliek, 'The Promises of Speeding Up'.

⁷⁴ Rots, Nynke and Els, Cécile van, 'Vaccinontwikkeling tijdens een pandemie: snel en toch zorgvuldig | RIVM' ['Vaccine development during a pandemic: proceeding quickly yet carefully | RIVM'].

⁷⁵ Corbett et al., 'mRNA-1273 Protects against SARS-CoV-2 Beta Infection in Nonhuman Primates'. Corbett, Kizzmekia S. et al., 'Immune Correlates of Protection by mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates'. Dai and Gao, 'Viral Targets for Vaccines against COVID-19'. Ravindran et al., 'Dynamics of temporal immune responses in nonhuman primates and humans immunized with COVID-19 vaccines'.

⁷⁶ RIVM, 'Infectieziektenbestrijding' ['Infectious disease control'].

⁷⁷ Minister of OCW, Voortgang onderzoek verdere verlaging proeven op niet-humane primaten (motie Wassenberg c.s.) [Progress of research into the further reduction of experiments on non-human primates (motion by Wassenberg et al.)].

are concerned. Autonomy is not a trivial matter: a great deal of scientific research is international, many projects are carried out by international research consortiums, and the exchange of scientific knowledge often takes place on an international scale. It is therefore pertinent to ask whether autonomy is at odds with the nature of scientific research: won't Dutch researchers always be able to collaborate internationally? Certainly where pandemic infectious diseases and vaccine development are concerned, we know since the Covid-19 pandemic that the opportunity to participate in international initiatives is not a given.⁷⁸ The important contributions that Dutch researchers made to the identification of Covid-19 and to vaccine development were made in the context of large international consortiums, but were possible only because of the researchers' own research experience, at their Dutch research facilities and capitalising on their international reputations.⁷⁹ At the moment, according to the virologists that the committee spoke to, NHPs are still necessary for research into new infectious diseases that threaten public health.⁸⁰ A Dutch NHP facility would therefore make a contribution to Dutch autonomy in the event of a new pandemic. That does not imply that NHP research cannot now be scaled back, but the committee makes the point that the consequent increased dependency on the international community is a risk, and that, when weighing up that risk, the unpredictable developments in geopolitical relations within Europe and with the US, Russia and China should be taken into account.

2.1.2 Life-threatening diseases and the importance of NHP research

The committee will first consider the possibility of defining the concept of 'life-threatening disease'. The various experts interviewed by the committee, both researchers and experts in the field of policy and implementation, said that 'life-threatening disease' is a concept used mainly in political debate; it is not precisely defined in scientific and clinical practice.⁸¹ Interviewees gave various examples of diseases that are serious but not life-threatening, such as Parkinson's disease and other brain diseases, untreatable cancers, genetic defects, cardiovascular diseases and diabetes. The reduction in lifespan will always depend partly on the concrete treatment options and host factors, including comorbidity.

In the scientific literature, a 'life-threatening condition' is defined as follows: *a condition that directly endangers the life of an individual and for which the prognosis is that it will most likely lead to death.*⁸² In NHP research practice, however, that definition is problematic. The likelihood of a condition being life-threatening depends on factors such as the severity of the condition, the availability of effective treatments and the health status of the individual. In addition, with some diseases, the prognosis may improve as a result of (clinical) scientific research. The following factors are also relevant:

- There are *several forms* in which a condition can be life-threatening. An illness or disease can lead to death directly, acutely, indirectly or delayed. For example, a chronic disease may not be life-threatening on its own, but in combination with other complications it may be life-threatening. Blindness, for example, is not itself life-threatening, but it can lead to life-

⁷⁸ See, for example, the Court of Audit's evaluation report on Dutch vaccine purchasing: Rekenkamer, 'Uit de pandemie. Onderzoek naar de aankoop van vaccins tegen COVID-19' ['Out of the pandemic. Research into the procurement of vaccines against COVID-19].

⁷⁹ Dutch researchers are internationally prominent in the field of research into how societies can respond resiliently to major crises. See, for example: PDPC, 'Pandemic & Disaster Preparedness Center'.

⁸⁰ In 2017, the Rathenau Institute also concluded that NHP research is necessary for infectious disease research: Rathenau Instituut, 'Van Aap naar beter. Een verkenning en dialoog over proeven met apen' ['From Primate to Wellness. An exploration of and dialogue regarding experimentation on primates']

⁸¹ The Population Screening Act (Wbo) refers to "serious diseases or abnormalities for which no prevention or treatment is possible". However, that definition is also inadequate. In a report, the Health Council observes that numerous factors play a role in determining whether a condition is 'serious' and advises the minister to explain the criterion 'serious' more fully. Gezondheidsraad, 'WBO: essentiële begrippen belicht' ['Population Screen Act: essential concepts explained'].

⁸² Andrykowski and Redd, 'Life-Threatening Disease Biopsychosocial Dimensions of Cancer Care'.

threatening situations, for example in traffic. Depression is not itself life-threatening, but it can lead to suicide when severe.

- Other relevant factors, in addition to the form, include *when* a condition threatens life, and *how many people* it threatens. If a disease is usually relatively benign, but life-threatening for certain people (e.g. because they have certain comorbidities), it is open to question whether the disease should qualify as life-threatening.
- It is also open to question whether the *suffering* associated with non-life-threatening diseases is necessarily less than that associated with life-threatening diseases. There are conditions that do not lead to death but cause great suffering; severe chronic pain is a good example.

The committee's conclusion that the criterion 'life-threatening' lacks a clear, scientific definition of the kind necessary for its use in the licensing of NHP research is similar to the Health Council's advice regarding the concept of 'serious diseases or abnormalities for which no prevention or treatment is possible' in the Population Screening Act, namely that the criterion 'serious' requires fuller and more explicit explanation.⁸³

If the criterion 'life-threatening' lacks a sound scientific basis, what is the alternative? An increasingly widely used concept is 'unmet medical needs', which relates to conditions for which no satisfactory means of diagnosis, prevention or treatment are available, or to circumstances where existing methods are inadequate or have significant drawbacks.⁸⁴ Consensus regarding the use of this concept is being sought at the European level as well. A few of the committee's interviewees expressed a preference for using that criterion for assessing the acceptability of NHP research. For the time being, however, the committee does not believe that 'unmet medical needs' would make a more workable criterion for use in the licensing of NHP research than 'life-threatening'. Furthermore, the adoption of 'unmet medical needs' as a criterion could lead to a wider range of NHP research being licensed, without any clear scientific parameters. Use of 'unmet medical needs' as a criterion might be possible in the future, if a way of quantifying the seriousness of medical needs can be agreed, opening the way for widely supported seriousness ranking.⁸⁵

Various other criteria for the licensing of NHP research have been proposed. The KNAW and the Rathenau Institute argue that research with NHPs should be legally permissible only if 'convincing and compelling reasons of scientific and societal interest' are involved.⁸⁶ However, that wording is not used in the Wod. The terms 'scientific interest' and 'societal interest' are mentioned in guidance on making licence applications to the CCD, however. Applicants are required to justify their proposed projects using those terms.⁸⁷ The distinction between scientific interest and societal interest is not unreasonable. 'Scientific interest' is often translated into basic scientific research: research aimed at building a broad understanding of phenomena. So, for example, research aimed at acquiring a better understanding of disease mechanisms, the brain or the immune system would come under that heading. Much behavioural research with NHPs also counts as basic scientific research. Research may be deemed to have 'societal interest' if it is important for public health.

⁸³ Gezondheidsraad, 'WBO: essentiële begrippen belicht' ['Population Screen Act: essential concepts explained'].: p. 15.

⁸⁴ Vreman et al., 'Unmet Medical Need'.

⁸⁵ Stokx, 'Defining Unmet Medical Need'.

⁸⁶ KNAW, 'Gebruik van niet-humane primaten (NHP) als proefdier. Nut of Noodzaak?' ['Use of Non-Human Primates (NHPs) as Laboratory Animals. Convenience of Necessity?']; Rathenau Instituut, 'Van Aap naar beter. Een verkenning en dialoog over proeven met apen' ['From Primate to Wellness. An exploration of and dialogue regarding experimentation on primates']

⁸⁷ CCD, 'Toelichting invullen formulieren aanvraag projectvergunning dierproef' ['Guidance on completing animal research project licence application forms'].

The committee concludes that none of the concepts considered are sufficiently well defined to serve as criteria for the licensing of NHP research. Nor, indeed, is the term 'life-threatening', as used in the committee's assignment. In its further exploration of this field, the committee will therefore refer to 'life-threatening and otherwise serious diseases'. It follows that, in the application of that criterion, a political choice must be made as to where the line should be drawn between serious and non-serious, and thus between diseases that may and may not be investigated by means of NHP research.

There are several sources that indicate that NHP research is still an important research model for the study of life-threatening and otherwise serious human diseases.⁸⁸ NHP research is still widely used in research areas where the complexity of human biology and disease processes are difficult to reproduce in other models and where ethical and practical considerations limit direct human research.⁸⁹ For testing the safety and efficacy of new medicines and treatments, NHPs are often considered necessary (after *in vitro* studies and/or studies with small animals), on the grounds that NHP responses to medicines or treatments are good predictors of human responses. In addition to infectious diseases, the US National Academies of Sciences mention research into Parkinson's disease, sickle cell anaemia, neurological conditions, immunotherapy and aging.⁹⁰

Opponents of NHP research often base their criticism on the following line of argument: there is growing evidence that the translatability of NHP models to humans is flawed.⁹¹ However, many researchers still consider that evidence shows the use of NHPs to be the most reliable method for researching complex conditions.⁹² The committee discusses the translatability issue further in section 2.4.

The European Commission's Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) published a report on experiments with NHPs in 2017.⁹³ The report states that, for some research areas – such as the development and safety assessment of medicines and medical devices, the treatment and prevention of infectious diseases, and neuroscience – NHP research is necessary. However, SCHEER does recommend that ethics committees approve NHP proposals only if there is no suitable alternative *and* a major scientific, medical or societal benefit can be expected. Furthermore, the data from NHP experiments and systematic reviews should be used more intensively by making them available in a public database. That would provide clarity as to the fields in which NHP models have proved unsuitable or have added little to existing knowledge regarding an illness. The report also argues that it is not desirable to prohibit essential research with NHPs in Europe, as the tests would then be carried out somewhere else, where there are fewer, if any, effective animal welfare safeguards. However, the harmonisation of regulations would make a significant contribution to the three Rs (see section 1.4.1), according to the SCHEER report.

⁸⁸ See, for example, Treue and Lemon, 'The Indispensable Contribution of Nonhuman Primates to Biomedical Research'.

⁸⁹ Sato and Sasaki, 'Genetic Engineering in Nonhuman Primates for Human Disease Modeling'.

⁹⁰ National Academies of Sciences, Engineering, and Medicine, *Nonhuman Primate Models in Biomedical Research*.

⁹¹ Leenaars et al., 'Animal to Human Translation'. NCad, 'Zienswijze: Afwegingskader voor het Prioriteren van Dierproeven voor Vervanging'. ZonMw, 'Kennisagenda Transitie naar Proefdiervrije Innovaties' ['Knowledge Agenda for the Transition to Animal-free Innovation']. Bailey and Balls showed that reports in the public media about medical breakthroughs due to NHP research are often exaggerated: Bailey and Balls, 'Clinical impact of high-profile animal-based research reported in the UK national press'. For an overview of the arguments against using NHPs in scientific research, see Bailey, 'Arguments Against Using Nonhuman Primates in Research'.

⁹² For an overview of the arguments in favour of using NHPs in scientific research, see Treue and Lemon, 'The Indispensable Contribution of Nonhuman Primates to Biomedical Research'.

⁹³ SCHEER, *Final Opinion on the Need for Non-Human Primates in Biomedical Research, Production and Testing of Products and Devices (Update 2017)*.

Nevertheless, SCHEER also acknowledges that a ban on NHP research could encourage research into alternatives (see chapter 4 of this report).

Analysis of the international literature shows that, at the global level, the main focus of NHP research into life-threatening and otherwise serious diseases is in brain research. The other major research areas are infectious diseases and vaccines, which were considered in the previous section of this report. [Figure 2](#) shows the primary research areas in which NHP research has been conducted globally, as identified by the literature analysis ([Appendix 1](#)). Behavioural and genetic studies and research into xenotransplantation and medicine safety are also included in this overview for illustrative purposes (as 'other').

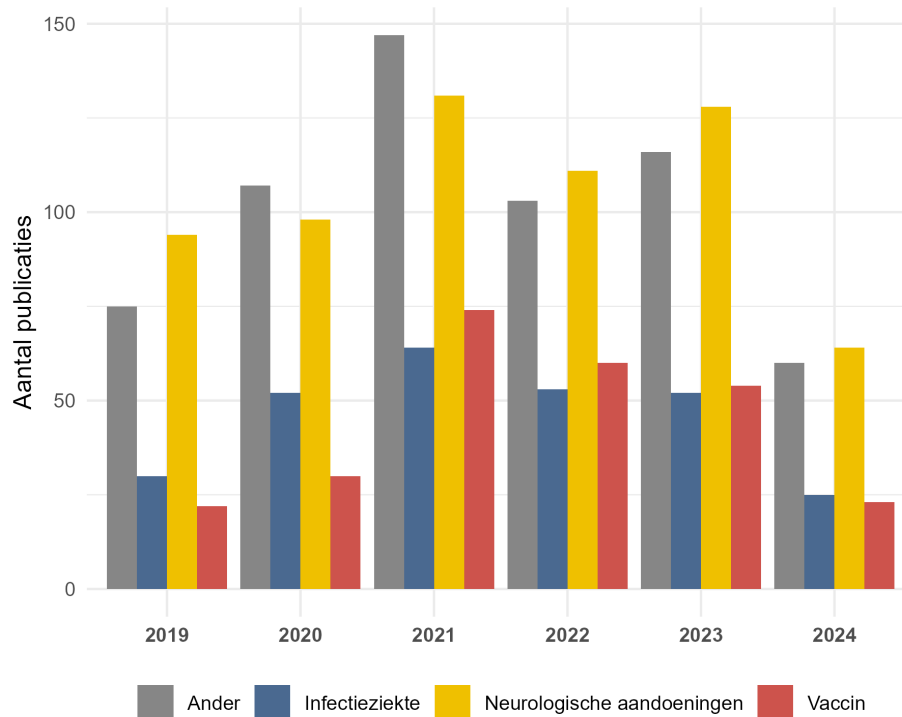


Figure 2 Overview of global NHP research by research area from 2019 to July 2024, inclusive (based on numbers of scientific publications).

The committee understands from experts that NHPs are frequently used in brain research and research into brain diseases because the structure and function of the NHP brain are very similar to those of the human brain. NHP studies are therefore done to improve understanding of complex neurological disorders such as Parkinson’s disease, Alzheimer’s disease and other neurodegenerative diseases. Such work is considered necessary by some researchers because little is yet known about how such conditions can be prevented or their progression slowed.⁹⁴ The complexity of the primate brain, like the human brain, cannot be adequately modelled by *in silico* or *in vitro* systems or by other animal species.⁹⁵ As the population ages, the burden of neurological disorders continues to rise, which some believe may lead to an even greater demand for NHP research in this field.⁹⁶ It should

⁹⁴ Eaton and Wishart, ‘Bridging the Gap’.

⁹⁵ For a comparison of the size and structure of the brains of different primates, see: Rilling, ‘Human and Nonhuman Primate Brains’.

⁹⁶ De Lima-Pardini et al., ‘Transcranial Magnetic Stimulation in Non-Human Primates’. Janssen et al., ‘Visualizing advances in the future of primate neuroscience research’.

nevertheless be noted that, in neurological research as well, use of human-centric models is increasing. From the trends revealed by the literature analysis, it is apparent that, at the global level, Parkinson's disease is the neurological disease for which NHPs are most often used. However, the positive developments in the field of deep brain stimulation for the treatment of Parkinson's disease have been achieved mainly on the basis of clinical experience, with some support from the findings of NHP research.⁹⁷

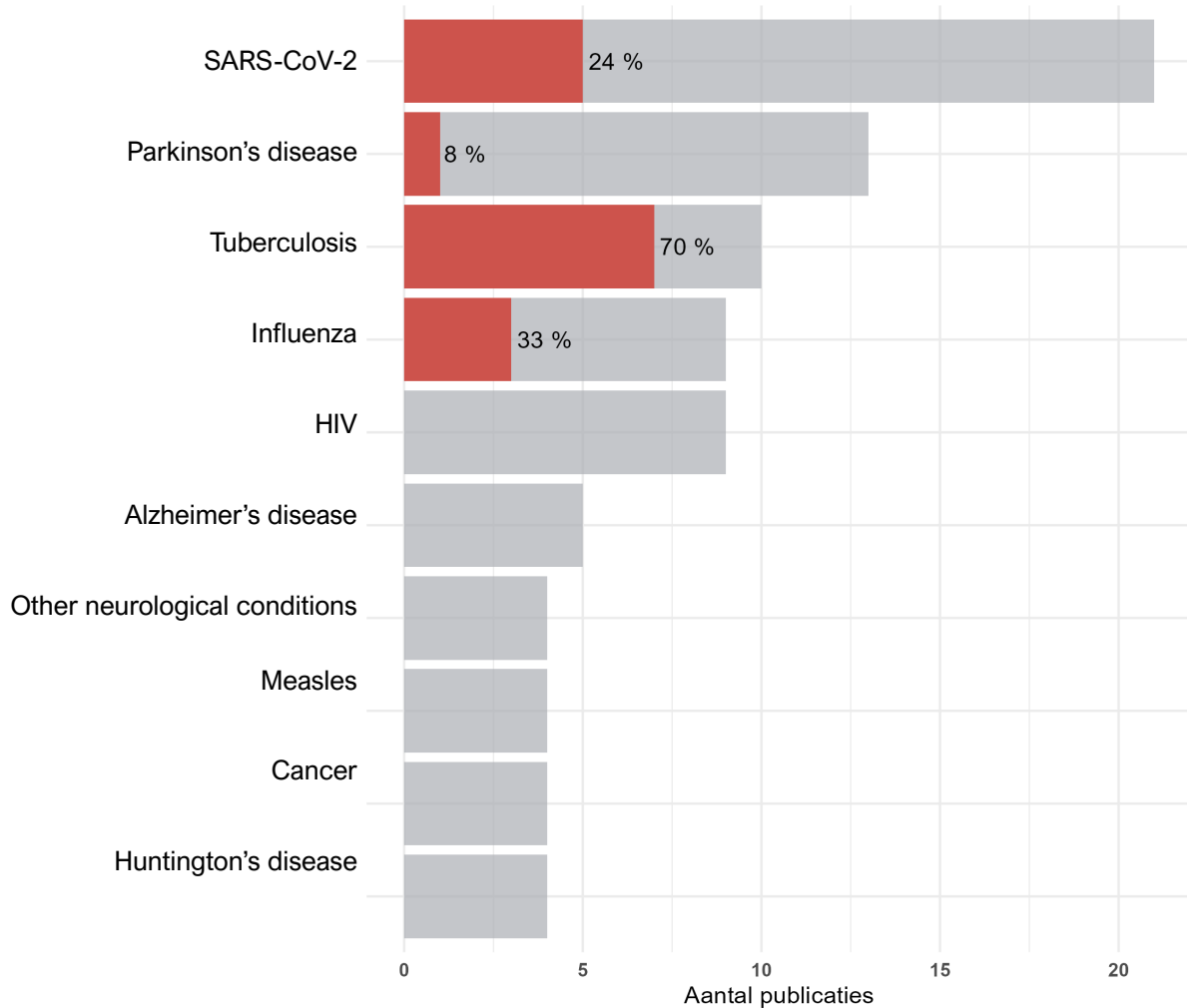


Figure 3 Overview of the top 10 disease areas where research was conducted using NHPs in the EU (grey) and the Netherlands (red) between 2019 and 2024 (based on numbers of publications).

2.1.3 Other scientific research with NHPs

Having considered infectious diseases that threaten public health and life-threatening and otherwise serious diseases, one category of research mentioned in the committee's assignment remains to be addressed, namely 'other scientific research with non-human primates'. Such research is mostly basic scientific research. However, there is some overlap between this category of research and research into life-threatening and otherwise serious diseases (see [Figure 3](#)). Although the European Animal

⁹⁷ Frey et al., 'Past, Present, and Future of Deep Brain Stimulation'. Gardner, 'A History of Deep Brain Stimulation'.

Experiments Directive and the Wod permit basic research (without specifying exactly what that means), experts in the field have advised the committee that, in the Netherlands, research with NHPs is in practice permitted only if the research is expected to have clear scientific benefit sufficient to justify the discomfort that the NHPs will experience.⁹⁸ Hence, where basic research is concerned as well, research is allowed only if a harm-benefit analysis convincingly demonstrates that, in due course, the results will be translatable to humans for the treatment of life-threatening and otherwise serious diseases. However, it is very difficult to determine in advance how far a basic research project will be translatable into practical applications. The CCD has indicated that it too finds that issue challenging.⁹⁹

The aim of basic research is to shed light on biological (disease) mechanisms, mostly at the cellular or molecular level. Examples include basic research into autoimmune diseases such as multiple sclerosis¹⁰⁰ and rheumatoid-arthritis¹⁰¹, genetic therapies and sight-restoring technologies.¹⁰² NHPs are also used for research into reproductive health because NHPs are very similar to humans in terms of their reproductive systems and developmental stages.¹⁰³ Such research is not undertaken in the Netherlands.

One example of the translation of basic research with NHPs into therapeutic developments is the discovery of mirror neurons in NHPs, leading to the development of therapies for people with chronic phantom pain in amputated limbs and to alleviate motor function problems in people with Parkinson's disease.¹⁰⁴ Another example is brain-machine interfaces, which were first studied in NHPs before being used to treat a patient with a transverse lesion.¹⁰⁵ Also, very recently, stem cell technologies originally tested in NHPs have been used to modify insulin-producing cells taken from diabetes patients, which were then successfully transplanted back into the patients.¹⁰⁶ Those examples illustrate the importance of prior NHP research, but also show that many such studies can now be continued using human subjects.

Another example of 'other scientific research' is a recent study in which the damaged heart of a seriously ill patient was repaired by means of stem cell transplantation.¹⁰⁷ Stem cells were activated in the laboratory to form heart tissue. It was necessary to investigate the possibility that the newly formed heart tissue might develop tumour cells. The German research team investigated that possibility using rhesus monkeys because NHPs are the only large mammals from which the relevant pluripotent stem cells can be cultivated. After safety testing on NHPs, the transplant procedure was successfully performed on a human subject. More generally, NHPs play an important role in mandatory product safety testing, i.e. research that is required by law to test the safety of new products before they are approved for sale. The products that require such testing include not only

⁹⁸ Wet op de Dierproeven (Wod, Animal Experiments Act). Section 10e, subsection 2, part b, and Section 1c, parts a and d.

⁹⁹ NCad, 'Verslag digitale bijeenkomst CCD/NCad 28-09-2020' ['Report on virtual CCD/NCad meeting 28-09-2020']. NCad, 'De projectbeoordeling van fundamenteel wetenschappelijk proefdieronderzoek' ['The review of animal research project proposals in basic scientific research'].

¹⁰⁰ 't Hart et al., 'Preclinical Models of Multiple Sclerosis in Nonhuman Primates'.

¹⁰¹ Vierboom et al., 'Pain Relief in Nonhuman Primate Models of Arthritis'.

¹⁰² NIN, 'Onderzoek' ['Research']. Chen et al., 'Shape Perception via a High-Channel-Count Neuroprosthesis in Monkey Visual Cortex'.

¹⁰³ Cauvin, Peters and Brennan, 'Advantages and Limitations of Commonly Used Nonhuman Primate Species in Research and Development of Biopharmaceuticals'.

¹⁰⁴ Deconinck et al., 'Reflections on Mirror Therapy'. Bonini et al., 'Mirror Neurons 30 Years Later'.

¹⁰⁵ Capogrosso et al., 'A Brain-Spine Interface Alleviating Gait Deficits after Spinal Cord Injury in Primates'. Lorach et al., 'Walking Naturally after Spinal Cord Injury Using a Brain-Spine Interface'.

¹⁰⁶ Du et al., 'Human Pluripotent Stem-Cell-Derived Islets Ameliorate Diabetes in Non-Human Primates'. Wang et al., 'Transplantation of Chemically Induced Pluripotent Stem-Cell-Derived Islets under Abdominal Anterior Rectus Sheath in a Type 1 Diabetes Patient'.

¹⁰⁷ Jebran et al., 'Engineered Heart Muscle Allografts for Heart Repair in Primates and Humans'.

human medicines, but also industrial chemicals and veterinary medicines.¹⁰⁸ Such research is permitted within the EU, but is no longer carried out using NHPs in the Netherlands.

Finally, behavioural studies are conducted with NHPs, which involve keeping the animals in captivity, but do not involve any physical discomfort for the animals. Behavioural research by Dutch researchers is an important activity within the BPRC. Another form of research carried out using NHPs involves non-invasive behavioural research to train the animals for participation in tasks or experiments. Such methods are designed to minimise stress or discomfort and can be used to investigate cognition, perception, and social interactions. Research of that kind does not qualify as an animal experiment, and no authorisation or registration is required. Even genetic research can be done without causing discomfort to the animals used as subjects. That is the case, for example, when DNA samples are obtained from hair or faeces in non-invasive ways.

2.2 International use of NHPs: countries, numbers and research questions addressed

Research on NHPs is not confined by national borders. There is a lot of international collaboration in the field of NHP research, with SARS-CoV-2 research being a good example. In order to provide a picture of NHP research around the world, the committee studied information that is publicly available in the EU and, as far as possible, elsewhere. The systematic review of academic articles also provides insight into the countries where NHP research is conducted, and into the numbers and research areas involved.

¹⁰⁸ Rathenau Instituut, 'Van Aap naar beter. Een verkenning en dialoog over proeven met apen' ['From Primate to Wellness. An exploration of and dialogue regarding experimentation on primates']

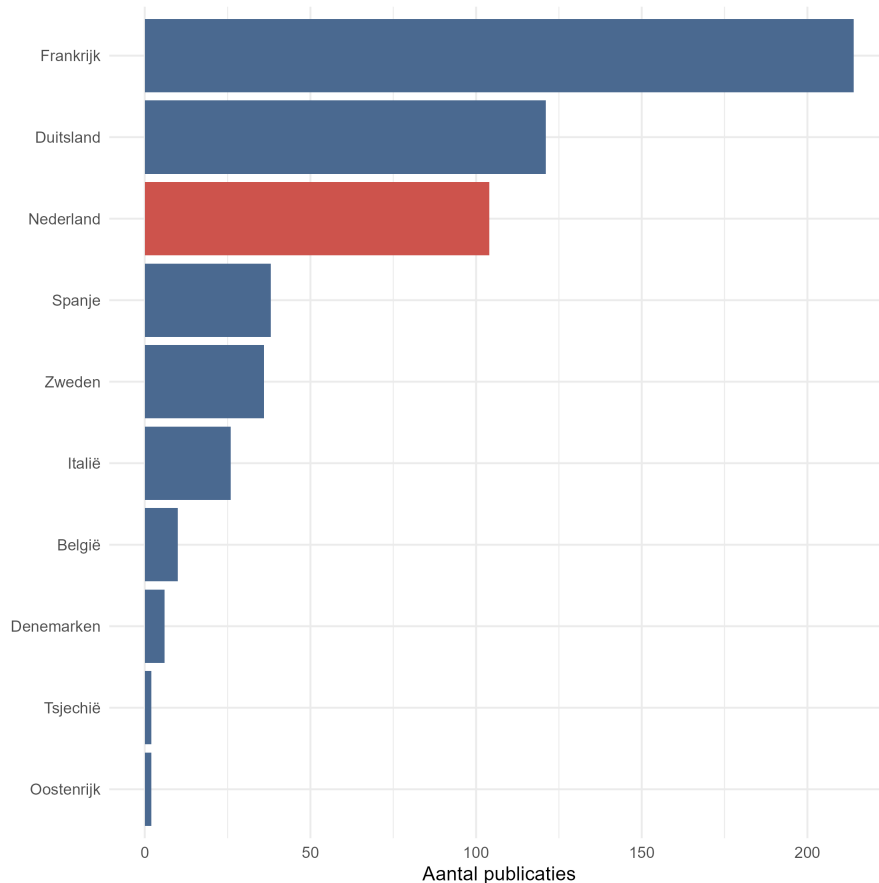


Figure 4 Number of NHP research publications per EU country from 1977 to July 2024, inclusive

Figure 4 shows how many NHP studies have been published in the various EU countries since 1977. After France and Germany, the Netherlands is the country with the most publications. The Netherlands is therefore a historically important player in NHP research (involvements) within the EU.

EU member states are required by EU Directive 2010/63/EU to provide annual statistics on the number of animals used in scientific research and the purposes of the procedures in question. The resulting data is stored in the ALURES database. Table 1 shows the number of experiments performed on NHPs in the EU, as recorded in the ALURES data for 2020.¹⁰⁹ The data for the other years is relatively consistent, so the table provides a good picture of the amount of NHP research taking place in the various EU member states. However, the totals for 2020 are likely to be higher than those for other years, because there was a peak in NHP use for SARS-CoV-2 research.

¹⁰⁹ CIRCABC, 'Summary report on the statistics on the use of animals for scientific purposes in the EU and Norway (2020)'.

Member state	Number of NHP experiments in 2020	Species
France	3,996	Long-tailed macaques, prosimians, Callitrichidae, vervets and baboons
Germany	2,031	Long-tailed macaques, prosimians, rhesus monkeys, long-tailed macaques, baboons, squirrel monkeys
Italy	504	Long-tailed macaques, rhesus monkeys
Spain	475	Long-tailed macaques
Netherlands	212	Long-tailed macaques, rhesus monkeys, Callitrichidae
Belgium	36	Rhesus monkeys, old world monkeys
Czech Republic	36	Long-tailed macaques, rhesus monkeys
Sweden	19	Long-tailed macaques and rhesus monkeys
Hungary.	2	Rhesus monkeys
Total	7,311	

Table 1 Number of experiments performed using NHPs in the EU in 2020

According to the ALURES database, 7,311 experiments were performed on NHPs throughout EU in 2020, involving 4,784 animals. The numbers of NHPs used in 2020, 2021 and 2022 were 7,311, 7,024, and 7,650, respectively. The numbers have not varied very much over the years. It is also apparent that research with NHPs is carried out only in a small number of EU member states, of which the Netherlands is one. NHPs are not used as laboratory animals in other countries.

Outside the EU, reliable (quantitative) information on animal testing with NHPs is often difficult to find. Some countries, such as the US, do publish data through the relevant ministries or government organisations. Despite leaving the EU, the UK follows the European legislation and publishes data on animal research. The number of experiments performed on NHPs in non-EU countries, insofar as can be established from public data sources, is summarised below. The summary draws on the most recent available data as far as possible.

- In the **United Kingdom (UK)**, **2,197** experiments were performed on NHPs in 2022. The animals used were mainly long-tailed macaques and to a lesser extent rhesus monkeys, marmosets and tamarins. The research in question was aimed at Parkinson's disease, infectious diseases, and the understanding of behaviour and the nervous system. The great majority of experiments on rhesus monkeys and long-tailed macaques are performed for medicine safety research, as required by the applicable regulations. Interestingly, the number of experiments on NHPs in the UK is trending downwards. In 2022, the number of experiments was the lowest since 2008.¹¹⁰
- There are seven National Primate Research Centers (NPRCs) in the **United States (US)**, where NHPs are bred. There are also many academic institutions and commercial organisations that house NHPs. In 2021, **70,300** NHPs were used for experiments in the US.¹¹¹ Statistics on animal research are published by the US Department of Agriculture. The

¹¹⁰ UK Home Office, 'Statistics of scientific procedures on living animals, Great Britain: 2022'.

¹¹¹ National Academies of Sciences, Engineering, and Medicine, *Nonhuman Primate Models in Biomedical Research*.

main objectives of the research were HIV prevention, insight into SARS-CoV-2, hepatitis C, cancer, Zika virus, Alzheimer's disease, Parkinson's disease and brain-machine interfaces.

- In **Switzerland**, animal research is performed on NHPs in Zurich and Fribourg.¹¹² In 2022, **200** experiments were performed on rhesus monkeys and long-tailed macaques. The experiments performed in Zurich were for neurological research purposes, while those carried out in Fribourg were for improved understanding of the motor, visual, auditory and reward systems and for the development of related therapies.¹¹³
- Research on NHPs also takes place in **Japan**, but no data is published. Japan has rules regulating the use of animals in research, but they are not binding. Researchers are encouraged to apply the principles of the three Rs (replacement, reduction and refinement), but there is considerable freedom as to how that is done. The number of NHPs used is not reported, and there is a tendency to prioritise researchers' academic freedom over animal welfare.¹¹⁴
- **China** has guidelines on the use of NHPs in research, but they are not legally binding and compliance is not enforced. There is a system of regional and provincial laws and policies, but research centres enjoy considerable freedom.¹¹⁵ China used to be an important player in the international trade in NHPs for research. In 2020, however, China decided to stop exporting monkeys for research (see [2.3](#)).

The academic literature review also looked into the countries that initiated research on NHPs.¹¹⁶ It was found that the Netherlands figured prominently, as the eighth most active nation globally and the third within the EU (see [Figure 5](#)).

¹¹² Office fédéral de la sécurité alimentaire et des affaires vétérinaires, 'Expériences sur animaux en 2022 en Suisse' [Animal experiments in Switzerland in 2022].

¹¹³ Swiss Non-Human Primates Competence Center for Research, 'Research at the University of Zürich'.

¹¹⁴ Central Institute for Experimental Medicine and Life Science, 'Introduction'.

¹¹⁵ National Primate Research Centers, 'A National Resource for the Scientific Research Community'.

¹¹⁶ The figures were established using the country where the last-named author works as a proxy, given that the last-named author is usually the party who initiated the research. For details, see the literature review by James Gallant in Appendix 1.

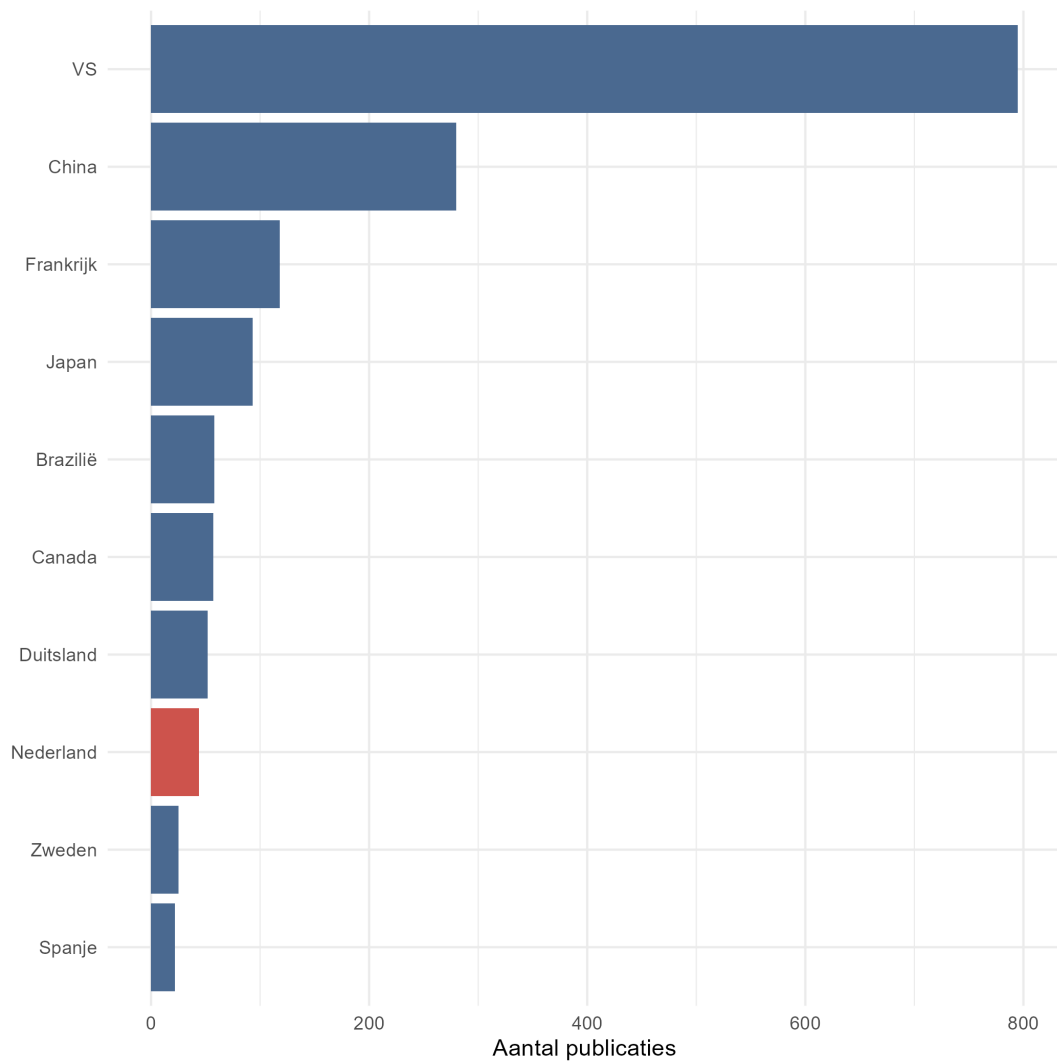


Figure 5 The ten countries worldwide that initiated the most research on NHPs between 2019 and July 2024, inclusive (based on publications' last-named authors)

2.3 International trends in scientific research involving NHPs

Our academic literature review revealed that research with NHPs has been increasing (Figure 6). That picture could also be attributable, to some degree, to other factors, such as a global rise in the total number of publications, an increase in international collaboration and greater availability of digital sources.

In the Netherlands, the BPRC's colony has been reduced in recent years. Elsewhere, however, particularly in China and the US, the use of NHPs for research has been increasing.¹¹⁷ The Dutch reduction in NHP research and the intention to reduce such research further are not therefore in line with the global trend; in fact, the opposite appears to be the case. Only the UK has also seen a decline in NHP research.

¹¹⁷ National Academies of Sciences, Engineering, and Medicine, *Nonhuman Primate Models in Biomedical Research*.

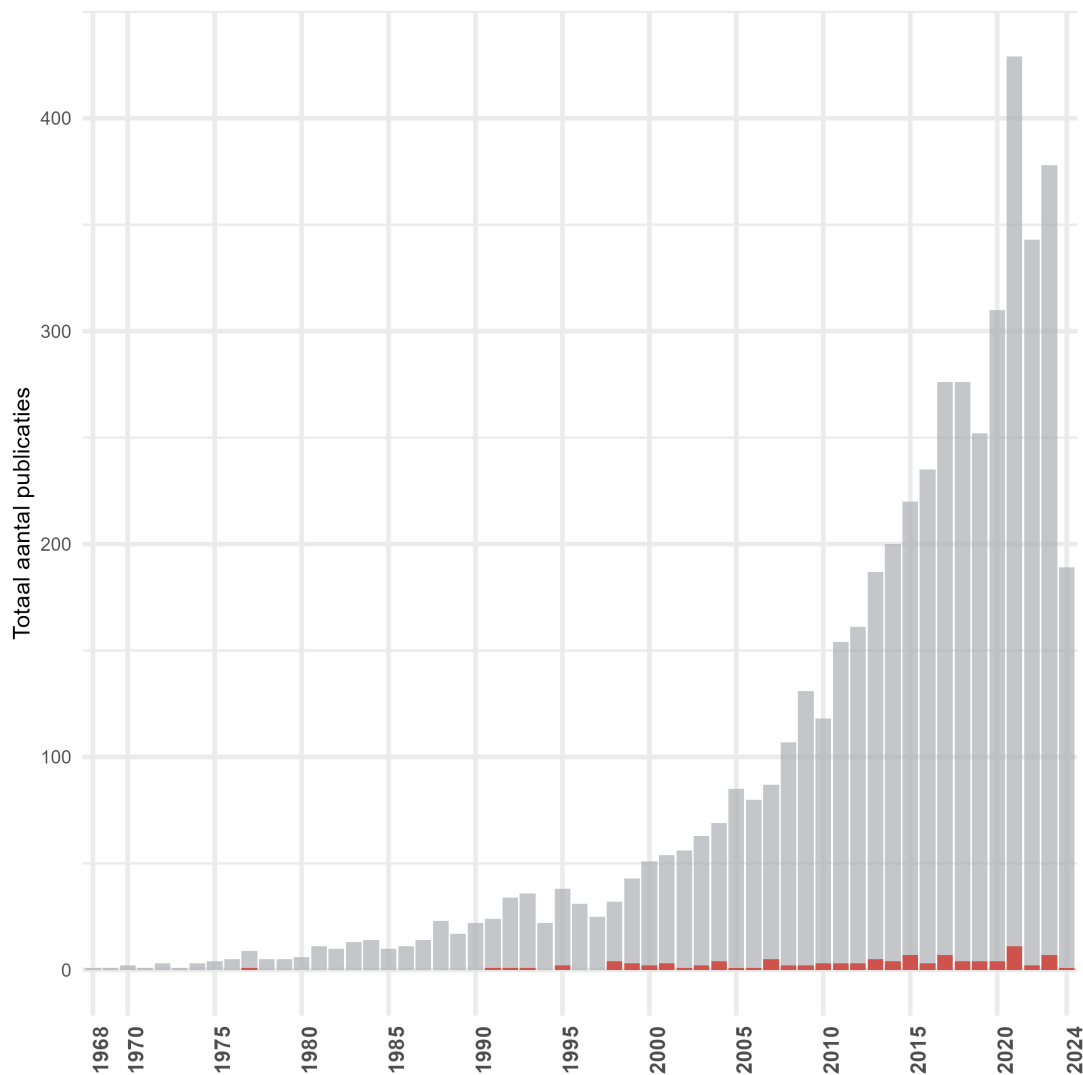


Figure 6 Annual number of NHP research-related publications worldwide

China used to be a major exporter of NHPs bred for research, but decided in 2020 to stop exportation. That led to a shortage of laboratory animals in the US and Europe, and to the available animals becoming more expensive. That in turn created a market for illegally traded NHPs. Some trafficked animals turned out to be wild monkeys with diseases.¹¹⁸ China's decision to end exports was linked to its own commitment to basic brain research, as manifested in the China Brain Project (CBP). Many NHPs will be used in the context of that project: in the future, around 20,000 monkeys will be housed in Hainan province alone.¹¹⁹ The US is also pressing ahead with NHP research and will try to become less dependent on imports in the future.¹²⁰ The state of Georgia will house around 30,000 monkeys over the next few years, which will be available to universities and other institutes for research.¹²¹

¹¹⁸ Conroy, 'How Wild Monkeys "Laundered" for Science Could Undermine Research'.

¹¹⁹ Normile, Dennis, 'China Bets Big on Brain Research with Massive Cash Infusion and Openness to Monkey Studies'.

¹²⁰ Harding (2017) provides a good overview, albeit written before the outbreak of the SARS-CoV-2 pandemic: Harding, 'Nonhuman Primates and Translational Research'.

¹²¹ Oliver Milman, 'Plan for US "mini-city" of 30,000 monkeys for medical research faces backlash'.

2.4 The issue of translatability of NHP research

The 'translatability' of animal research is the extent to which it yields results that can be expected to be relevant for subsequent research in humans. Such translatability is very difficult to predict in practice.¹²²

NHPs are often used as models in scientific research because of their similarity to humans. The research in question is mainly into infectious diseases and brain diseases, but also into new developments in organ and tissue transplantation and implantation.¹²³ Technological and genetic advances also make it possible to genetically modify NHPs in order to mimic human diseases more accurately. However, strict regulatory restrictions make it very difficult to perform such research in the Netherlands or elsewhere in the EU.¹²⁴ By using such techniques, researchers are able to obtain a more accurate picture of disease development and the efficacy of treatments in a context that closely resembles the human context. Nevertheless, the use of NHPs is not necessarily beneficial for the investigation of all scientific issues. Furthermore, there is growing doubt regarding the direct translatability of research findings from NHPs to humans.¹²⁵ In 2019, Ferreira et al. developed a framework for optimal animal modelling for the investigation of medicine efficacy.¹²⁶ In a related publication, one of the same authors' conclusions was that, despite the biological similarity of NHPs to humans, the indiscriminate use of NHPs for testing the safety of new biotech products often adds little of value to the body of preclinical research findings.¹²⁷

Other criticism of the assumption that NHP model findings are translatable to humans has been expressed.¹²⁸ Ineichen et al. (2024) conclude from their meta-analysis of scientific literature that about 50 per cent of therapies from animal studies (i.e. not only from NHP studies) progress to human studies; some 40 per cent progress to randomised controlled trials (RCTs), and only 5 per cent are ultimately approved by regulatory bodies. That is in line with clinical research outcomes in general: there is a funnel pattern, with more and more possible therapies falling by the wayside as the development process progresses. This gap between basic research and ultimately validated therapies is a general phenomenon also known as the 'valley of death'.¹²⁹ Research by Leenaars et al., published in 2019, also shows that it is very difficult to predict what percentage of animal studies will be successfully translated into human clinical trials, with actual rates varying from zero to 100 per cent.¹³⁰ Nevertheless, it is also important to recognise that all current therapies have emerged from the funnel and that basic research and animal research are filtering out potentially harmful therapeutic applications by, for example, filtering out those that have unexpected side-effects observed in animal models. However, the opposite may also occur: adverse animal research findings may lead to clinical trials not going ahead, when in fact the treatments might have worked in

¹²² Ineichen et al., 'Analysis of Animal-to-Human Translation Shows That Only 5% of Animal-Tested Therapeutic Interventions Obtain Regulatory Approval for Human Applications'. Leenaars et al., 'Animal to Human Translation'.

¹²³ Aid et al., 'Mpox Infection Protects against Re-Challenge in Rhesus Macaques'. Albrecht et al., 'COVID-19 Research'.

Anderson and Kirk, 'Primate Models in Organ Transplantation'. Belloir et al., 'Large-Scale Multimodal Surface Neural Interfaces for Primates'. von Bibra and Hinkel, 'Non-Human Primate Studies for Cardiomyocyte Transplantation – Ready for Translation?' Eaton and Wishart, 'Bridging the Gap'. Manook et al., 'Prolonged xenokidney graft survival in sensitized NHP recipients by expression of multiple human transgenes in a triple knockout pig'. Scanga and Flynn, 'Modeling Tuberculosis in Nonhuman Primates'. Dam and De Deyn, 'Non-Human Primate Models for Alzheimer's Disease-Related Research and Drug Discovery'.

¹²⁴ Liang et al., 'Gene Editing Monkeys'.

¹²⁵ Bailey and Taylor, 'Non-Human Primates in Neuroscience Research'.

¹²⁶ Ferreira et al., 'A Standardised Framework to Identify Optimal Animal Models for Efficacy Assessment in Drug Development'.

¹²⁷ Meer et al., 'The Ability of Animal Studies to Detect Serious Post Marketing Adverse Events Is Limited'.

¹²⁸ Knight, 'A Critique of the Bateson Review of Research Using Non-Human Primates'. Bateson, 'Review of Research Using Non-Human Primates'. Lindl, Völkel, and Kolar, 'Animal Experiments in Biomedical Research. An Evaluation of the Clinical Relevance of Approved Animal Experimental Projects'.

¹²⁹ Seyhan, 'Lost in translation'.

¹³⁰ Leenaars et al., 'Animal to Human Translation'.

humans. For example, aspirin and paracetamol probably would not have reached the market for human use if they had first been tested on dogs, because both substances are toxic for dogs.

Various parties from the research world interviewed by the committee confirmed that within the scientific community there is a growing sense that the translatability of animal research results to humans is limited. That is particularly the case where the use of mice and rats (and, to some extent NHPs) is concerned, partly because of anatomical and physiological differences. For example, laboratory mice are often housed under sterile conditions, which significantly influence their immune systems and the way that their bodies respond to external stimuli and their comparability to humans.

Also, researchers are increasingly focusing on how medicines and treatments affect people with particular characteristics, and less on their generic effects (how they affect the human population as a whole). Also, a study performed using wild NHPs from a natural environment may yield different results from a study performed using disease-free NHPs reared in a primate centre, which are on a standard diet and are free of comorbidity, such as parasitic infections. Furthermore, NHPs live under very different circumstances than humans, which may also influence research findings. Consequently, the translatability of animal research results to humans is always subject to limitations.

Nevertheless, some NHP models offer particular anatomical, physiological, genetic, immunological, pathological or behavioural similarities to humans that are sufficiently great to make them very suitable for the study of certain human diseases.¹³¹ For example, the routes by which viruses gain entry and the organ systems and cell types they infect are often similar in NHPs to those in humans.¹³² Nevertheless, the translational value of the findings is determined by various other factors as well, such as the (limited) similarity between disease processes in humans and NHPs.¹³³ Lack of knowledge about the underlying biology can therefore be an obstacle to choosing an appropriate model.

Some interviewees indicated that more research is needed into the translatability of NHP research to humans. When are experiments on NHPs necessary to safely demonstrate the effect on humans? When is research with rats or alternatives to animal research sufficient? And do such alternatives provide sufficient insight into the effects on people?¹³⁴ Others argue that there are diseases for which NHPs are still clearly the best model for investigating, for example, disease-specific pathology or systemic effects on different organ systems. In addition, the translatability of even the best available animal models (including humans) is never perfect, leading to questions about the need for animal models in general, as well as the translatability of other models. While important, the discussion of such questions is outside the committee's remit.

The field of TB research clearly illustrates the dilemmas surrounding the translatability of NHP models. NHPs represent the most relevant model for studying the infectious disease tuberculosis: there is still no effective vaccine against TB, which is the world's most deadly infectious disease. Meanwhile, resistance to the standard antibiotics (MDR/XDR: multi-drug resistance and extensive

¹³¹ Phillips et al., 'Why Primate Models Matter'. Janssen et al., 'Visualizing advances in the future of primate neuroscience research'. 't Hart, Laman, and Kap, 'An Unexpected Symbiosis of Animal Welfare and Clinical Relevance in a Refined Nonhuman Primate Model of Human Autoimmune Disease'.

¹³² Estes, Wong and Brenchley, 'Nonhuman Primate Models of Human Viral Infections'.

¹³³ For a wide-ranging discussion of animal models in translational research, see: Denayer, Stöhr and Roy, 'Animal models in translational medicine'.

¹³⁴ The 90 to 93 per cent genetic similarity between NHPs and humans is in itself an insufficient basis for assuming that NHP research findings are readily translatable to humans: Bailey, 'Monkey-Based Research on Human Disease'.

drug resistance) is becoming a serious problem in the Netherlands as elsewhere. NHP models have provided considerable insight into disease mechanisms, such as the cell structures in the lung where the bacteria remain concealed and are difficult for medicines to reach, and into mucosal vaccination methods.¹³⁵ However, an NHP model is also of limited value for TB research. A clinical trial in children found that the translatability of NHP models is limited by the fact that humans reach immunological maturity later than NHPs. The trial found that a vaccine boost strategy that provided increased protection in adult NHPs did not have the anticipated effect in human children.¹³⁶ The trial in question and the follow-on research did, however, demonstrate that in vaccine research it is necessary to look at other indicators of immunity ('correlates of protection') in NHP and humans than those studied in the past.

Finally, real-life scenarios in humans, such as comorbidities (e.g. TB and diabetes) are difficult to model in NHPs. As a result, clinical studies with human subjects can yield different results from those obtained from studies with NHPs. Because the number of NHPs used in an experiment is often small (sometimes as few as six animals are used), the findings may not be relevant for all the humans involved in subsequent clinical trials. If, for example, the trials involve older people or people with various co-morbidities, side-effects may occur that were not observed in the NHPs.

¹³⁵ Dijkman et al., 'Prevention of Tuberculosis Infection and Disease by Local BCG in Repeatedly Exposed Rhesus Macaques'. Dijkman et al., 'Pulmonary MTBVAC Vaccination Induces Immune Signatures Previously Correlated with Prevention of Tuberculosis Infection'.

¹³⁶ Verreck et al., 'MVA.85A Boosting of BCG and an Attenuated, *phoP* Deficient *M. Tuberculosis* Vaccine Both Show Protective Efficacy Against Tuberculosis in Rhesus Macaques'. Tameris et al., 'Safety and Efficacy of MVA85A, a New Tuberculosis Vaccine, in Infants Previously Vaccinated with BCG'.

3 NHPs in the Netherlands

This chapter provides an overview of research with NHPs in the Netherlands. The first section discusses the NHP facilities in the Netherlands. The following section summarises the number of NHPs used in the Netherlands and the trend in those numbers. Section 3.3 then examines NHP research in the Netherlands, covering topics such as the research agenda, research practice, ethical review and the degree of discomfort experienced by NHPs. The final section considers the importance of Dutch NHP research in an international context, focusing on the geopolitical aspects of NHP use.

3.1 NHP facilities in the Netherlands

In the Netherlands, NHP research is currently undertaken at two research facilities: the Biomedical Primate Research Centre (BPRC) in Rijswijk and the Netherlands Institute for Neuroscience (NIN) in Amsterdam.

The BPRC is the primate centre for biomedical research with NHPs in the Netherlands.¹³⁷ The BPRC is a public entity that breeds its own laboratory animals and maintains its own research programme. The BPRC was originally part of the Netherlands Organisation for Applied Scientific Research (TNO), but in 1994 the TNO Primate Centre became an independent foundation with its own board. The BPRC's mission is to contribute to public health through scientific research into serious human diseases. That includes developing new therapies, vaccines and treatment methods, within the ethical and legal parameters outlined above.

In 2024, the BPRC workforce was 99.1 FTEs, from animal handlers and veterinarians (42.7 FTEs) to scientific researchers (40 FTEs) and administrative staff (16.4 FTEs). Those personnel work in a number of departments: Laboratory Animal Science, Parasitology, Virology, Comparative Genetics & Refinement, Neurobiology & Ageing. The organisation is governed by an Executive Team and a Supervisory Board. There is also a Scientific Advisory Board made up of experienced researchers from universities and other institutions.

Funding for the BPRC comes mainly from the public purse. The main source of income for the BPRC is a grant from the Dutch government. For 2024, the BPRC received about €12 million from the Ministry of Education, Culture and Science (OCW). No fixed portion of this grant is earmarked for animal-free research and testing methods. However, the BPRC does inform the Minister of OCW about how its research budget is allocated. The portion of the OCW grant spent on animal-free research and testing methods was 14.1 per cent (€1.6 million) in 2020, 17.7 per cent (€1.9 million) in 2021, 16.4 per cent (€1.9 million) in 2022 and 18.5 per cent (€2.2 million) in 2023. The minister has agreed with the BPRC that in 2024 and 2025, the percentage of the grant spent on animal-free research and testing methods will remain at least 17 per cent.

In addition to the government grant, the BPRC needs about €5 million every year to perform its role. Most of the additional money comes from external project revenues. The main external sources are the EU (€2.85 million), the US National Institute of Health (NIH), and funding bodies such as the Bill and Melinda Gates Foundation (€0.65 million). Some of the research in question is 'precompetitive'

¹³⁷ BPRC, 'Biomedical Primate Research Centre'.

research.¹³⁸ Precompetitive research is not commercial contract research, but involves collaboration with pharmaceutical partners and/or other research institutes, through which the BPRC is an active scientific contributor to vaccine and medicine development.¹³⁹ All research carried out at the BPRC (including the precompetitive research) and all data obtained from such research (therefore including data unfavourable to the research or contradictory data) are published in scientific journals or on appropriate websites. Such research is also always subject to peer review.

The BPRC conducts NHP research using monkeys that it breeds itself. Rhesus monkeys and long-tailed macaques originate from Asia and marmosets from South America, but have been bred in Rijswijk for many generations. That removes the need to transport animals from breeding centres in Asia, South America and elsewhere. If more animals of a particular species are needed than have been bred internally (an exceptional occurrence), or if animals are needed to increase the genetic diversity of its colony, the BPRC sometimes buys monkeys from other specialised breeding centres in Europe. No monkeys caught in the wild are ever acquired: that is not allowed under European regulations.

The BPRC carries out a wide range of research aimed at understanding and controlling serious human diseases. Analysis of the international literature shows that the BPRC is productive. Indeed, it is the most productive primate research centre in Europe for academic NHP research, followed by the German primate research centre. Some of the key research areas it works in are:

- Infectious diseases: research into infectious diseases such as malaria, tuberculosis and HIV/AIDS, for vaccine and medicine development. This is an important line of research for the BPRC.
- Neurological diseases: research into diseases such as Parkinson's disease and Alzheimer's disease is intended to support the development of new therapies or treatment methods, and to increase understanding of the pathophysiology of such conditions. In addition, a lot of the neurological and ageing research currently focuses on 'long Covid' associated with brain damage caused by SARS-CoV-2.
- Autoimmune and inflammatory diseases: research into conditions such as multiple sclerosis and rheumatoid arthritis to support the development of new treatment strategies.
- Transplant research: research into improving organ and tissue transplants by reducing rejection after transplantation.
- Occasionally, the BPRC also conducts research into cancer-related questions.
- Alternatives: research into the refinement of NHP experiments, *in vitro* models and animal welfare. A cross-departmental platform for animal-free innovations has been set up, which is linked to all the scientific research departments. The platform is intended to maximise cooperation and interaction in the field of animal-free innovation. Every science department has a PhD student working on an animal-free topic (*in vitro*, biobanks). A bioinformatician is also employed to develop models that can determine, before an experiment begins, whether an animal is suitable for a particular type of study (e.g. by determining certain resistances in advance). In terms of capacity, such activities account for about fifteen of the 47.2 full-time equivalents assigned to scientific research. The personnel in question include PhD researchers, PhD students and analysts.

¹³⁸ In the context of the BPRC's budget, 'precompetitive research' is research done by pharmaceutical partners in the context of medicine or vaccine validation, usually through EU or NIH consortia.

¹³⁹ The BPRC cannot currently apply directly to NWO or ZonMw for research funding. That hampers its ability to function as an independent research institute – both for NHP research and NAM research – and makes it difficult to attract young researchers.

- Ethological research: behavioural research is conducted to improve understanding and management of the colony and to support the NHP experiments. In addition, the NHPs at the BPRC are available for basic ethological research, most of which is carried out by external university researchers.

With regard to the work done in the 'Alternatives' research area, several experts from outside the BPRC expressed the view that the research activities are too isolated, and that much could be gained from more collaboration with university researchers specialising in NAMs. In that context, it would also be helpful if the BPRC were allowed to apply directly to NWO and ZonMw for funding in the role of principal investigator.

The circumstances under which NHPs are housed at the BPRC comply with the applicable European standards.¹⁴⁰ The BPRC additionally adheres to the stricter guidelines of the British 3R Centre.¹⁴¹ There is an increasing tendency, at the BPRC as elsewhere, for an approach based on the 'five freedoms' to be replaced by an approach based on the five domains of positive well-being.¹⁴²

The BPRC has often been the focus of political and public attention over the years (see also [1.2](#)). In response, the institute made reductions and adjustments to improve animal welfare and reduce animal research. In 2019, the BPRC was ordered by the Ministry of Education, Culture and Science to reduce the number of primate experiments by 40 per cent between 2020 and 2025 (to an average of 120 to 150 per year), and to reduce the breeding colony (from 1,500 primates in 2019 to around 1,000 in 2025). The breeding colony has already been reduced to 968 in recent years (by the end of 2023). The BPRC conducted 180 animal experiments in 2022 and 144 in 2023. The BPRC has indicated it will also reduce the number of animal experiments to the number desired by the Ministry of Education, Culture and Science by 2025, mainly by not accepting a number of externally funded assignments, but also by the development of *in vitro* methods to replace animal experiments.¹⁴³

An important caveat to the reduction order is that the breeding colony at the BPRC cannot be reduced much further without affecting the quality and reliability of the scientific research carried out there. The current BPRC colony is already relatively small, consisting of around 1,000 primates living in groups segregated on the basis of species. The colony is currently large enough to maintain an *outbred* primate population, meaning that it has sufficient genetic diversity. Genetic diversity is essential to avoid inbreeding, which would compromise animal health and undermine the validity of research models.¹⁴⁴

If the Netherlands decides to stop as much NHP research as possible, but to maintain a minimal colony of NHPs in case a pandemic occurs, the research capacity needed to undertake such research into pandemic infectious diseases will need to be maintained as well. Such research capacity – consisting of animal handlers, researchers, analysts and laboratory facilities – should remain active in order that it can be mobilised quickly in the event of a pandemic. That can be achieved by continuing research into infectious diseases. Maintaining a minimal colony in readiness for pandemic situations

¹⁴⁰ European Parliament and Council, 'Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the Protection of Animals Used for Scientific Purposes'.

¹⁴¹ NC3R, 'NC3Rs Guidelines: Non-human primate accommodation, care and use'.

¹⁴² The 'five freedoms' are: (1) freedom from thirst, hunger and malnutrition, (2) freedom from discomfort, (3) freedom from pain, injury and disease, (4) freedom to express natural behaviour, and (5) freedom from fear and distress. The five domains of animal well-being are: nutrition, environment, health, behaviour and mental state. Robinson and Weiss, *Nonhuman Primate Welfare*.

¹⁴³ Minister of OCW, 'Dierproeven' [Animal Research].

¹⁴⁴ For a general discussion of the management of NHP colonies for breeding and scientific research, see: Hobson, 'Safety Assessment Studies in Nonhuman Primates'.

makes sense only if appropriate research capacity is also maintained and remains active. The second research facility where NHP research takes place is the NIN.¹⁴⁵ The brain research carried out at the NIN using NHPs focuses on the visual system.¹⁴⁶ The NIN is part of the KNAW and has a dedicated primate unit with sixteen to twenty rhesus monkeys. The monkeys are used for basic research into visual observation, attention and awareness. The NHP research in question is funded by various grants and various funding providers: NWO, ZonMw, EU grants and donation-funded charities.

In 2019, the Ministry of Education, Culture and Science investigated the possibility of pooling the NHP research activities of the NIN and the BPRC. The conclusion was that this particular type of research is better done at the NIN in order to maintain the connection with other brain researchers, and because of the specialised equipment that the NIN has. It is worth noting that, as early as 2009, the desirability of the KNAW maintaining its own facility for NHPs was being debated within the organisation. Those in favour of closing the facility point to the prevailing sentiment of the Dutch parliament and public opinion regarding the phasing out of NHP research. Others highlight the conclusion of the 2019 ministerial report, namely that this particular type of research is better done at the NIN in order to maintain the connection with other brain researchers, and because of the specialised equipment that the NIN has. If NHPs were moved to the BPRC, it would be more difficult to make connections with other brain research.

A third research facility that plays an important role in relation to NHP research is the Erasmus Medical Centre (Erasmus MC). Although no primates are currently kept at the Erasmus MC, the centre does have a licence and facilities for NHP research. In fact, the Erasmus MC has a laboratory whose biosafety level (BSL) is 3+. (It was built to BSL4 standards, but has not been registered as BSL4; work is currently done at BSL3. BSL4 is required for research involving the Ebola virus or the Marburg virus, for example.¹⁴⁷) The laboratories with the highest BSL at the BPRC are BSL3. In the event of a threat from an emerging infectious disease, the Erasmus MC's project licence could be used. The licence has been pre-approved by the CCD. If the Erasmus MC's licence were activated, primates from the BPRC would be made available to the centre, and any NHP research carried out at the Erasmus MC would be supervised by BPRC veterinarians. Under such circumstances, the animals would remain in Rotterdam for 2-3 weeks until being euthanised during or following the research.

Radboud University had an NHP facility until 2016, but the accommodation systems and expertise are no longer present. The Nijmegen-based brain researchers now have collaboration agreements with the BPRC and the NIN, and they carry out their research at those centres. For example, Radboud University's Donders Institute conducts research into human cognition and behaviour in health and disease. A number of researchers are working on neurotech applications (such as cochlear implants, visual implants and brainstem implants), for which they wish to carry out NHP experiments.

¹⁴⁵ NIN, 'Nederlands Herseninstituut - Master the mind'.

¹⁴⁶ See, for example, Roelfsema and Treue, 'Basic Neuroscience Research with Nonhuman Primates'.

¹⁴⁷ Adams, Muchmore, and Richardson, *Non Human Primates in Biomedical Research*.

3.2 NHPs used in the Netherlands: trend in numbers over the past ten years

In this section, the committee outlines the trend in the use of NHPs for scientific research. In the Netherlands, 144 primates were used for research in 2023 (see Table 2).¹⁴⁸

	2019	2020	2021 ¹⁴⁹	2022	2023
Callitrichidae	0	25	2	5	5
Rhesus monkeys	117	159	200	145	117
Long-tailed macaques	38	28	13	32	22
Total	155	212	215	182	144

Table 2 Number of NHPs used for research in the Netherlands 2019-2023

The great majority of NHP experiments take place at the BPRC. In addition, a small number of NHP experiments are carried out at the NIN (in 2022, for example, just two experiments were performed). The NHPs in question are used mainly for applied scientific research and, to a lesser extent, for basic research. In contrast to what happens in other countries, NHPs are not used for toxicological research in the Netherlands. The number of NHP experiments carried out fluctuated in the years 2019 to 2023. The increase in the period 2020 to 2021 was related to SARS-CoV-2. It is therefore important to look further back in time in order to discern an underlying trend. A clear decrease in the use of NHP experiments is then evident (see Table 3).¹⁵⁰

	1995	1999	2011	2023
Total number of NHP experiments (university research centres, KNAW institutions, BPRC)	857	620	345	144

Table 3 Number of NHPs used for research in the Netherlands 1995, 1999, 2011, 2023.

Researchers are required to indicate the degree of discomfort caused in the NHP research they conduct (see section 1.5). The studies carried out in the Netherlands in 2023 resulted in mild and moderate discomfort for the animals (ninety-two cases of mild discomfort, forty-seven cases of moderate discomfort).¹⁵¹ Analysis of the international literature shows a global increase in the use of non-invasive techniques in primate models; that was also the case in the Netherlands. The Netherlands does report a higher number of infectious disease studies involving the use of NHPs in 2021. An increase in the amount of discomfort caused can therefore be seen in 2021 due to the SARS-CoV-2 pandemic.

¹⁴⁸ Research with NHPs accounts for a very small proportion of all animal research in the Netherlands (0.04 per cent). In 2023, 351,872 animal experiments were recorded in the Netherlands, carried out by seventy-seven licence holders. NVWA, 'Zo doende 2023: Jaaroverzicht dierproeven en proefdieren van de Nederlandse Voedsel- en Warenautoriteit' ['Doing it that way 2023: Netherlands Food and Consumer Product Safety Authority annual report on animal research and laboratory animals'].

¹⁴⁹ This increase can be explained by SARS-CoV-2

¹⁵⁰ KNAW, 'Gebruik van niet-humane primaten (NHP) als proefdier. Nut of Noodzaak?' ['Use of Non-Human Primates (NHPs) as Laboratory Animals. Convenience of Necessity?']

¹⁵¹ NVWA, 'Zo doende 2023: Jaaroverzicht dierproeven en proefdieren van de Nederlandse Voedsel- en Warenautoriteit' ['Doing it that way 2023: Netherlands Food and Consumer Product Safety Authority annual report on animal research and laboratory animals'].

In that context, it is notable that the management of NHP research in the Netherlands is currently based on the number of animal experiments, with no distinction made on the basis of the degree of discomfort involved. In addition, it is common for experiments to be terminated before severe discomfort occurs. In such cases, the NHP is normally euthanised (a so-called 'humane endpoint'). Because the animals in question are prematurely removed from the research, that is not reflected in the discomfort data.

3.3 NHP research in the Netherlands

From the analysis of Dutch primate centres and interviews with researchers, it is apparent that experiments with NHPs are currently conducted in several research domains. From the information gathered, it is possible to deduce a (largely implicit) agenda for research with NHPs. Researchers in various domains are seeking to understand diseases better, as a basis for contributing to the development of (more) effective and/or safe medicines, vaccines and treatment methods. In the *domain of infectious diseases*, research is being conducted in the Netherlands into diseases such as malaria, dengue, Zika virus, Rift Valley fever, hepatitis, West Nile virus, tuberculosis, HIV/AIDS, rabies, influenza and SARS-CoV-2. Although knowledge regarding existing infectious diseases is increasing all the time, appropriate medicines and/or vaccines are not yet available everywhere. Furthermore, emerging infectious diseases require new vaccines and medicines. In the *neuroscience domain*, NHP research is conducted into Parkinson's disease, Alzheimer's disease and blindness. Parkinson's disease and Alzheimer's disease require new therapies and treatment methods. Because the number of people suffering from those diseases around the world is increasing as a consequence of population ageing, the need for such therapies and treatment methods is increasingly pressing. However, as the committee demonstrates in this report (see, for example, section 2.4), it is not clearly the case that NHP research is of particular value in that context compared with other experimental approaches. NHP research is being carried out into the treatment of blindness by means of brain implants, which have the potential to yield new treatment opportunities. Many questions remain to be answered regarding the development and treatment of *autoimmune and inflammatory diseases* such as multiple sclerosis and rheumatoid arthritis. The course of such diseases differs from patient to patient and is difficult to predict, due to the complex interactions between the various parts of the nervous system. In the *transplant domain*, research is being conducted to improve organ and tissue transplants by controlling rejection after transplantation. Such research, some of which involves the use of NHPs, is still at a dynamic stage of development.

Since the introduction of the three Rs in European and Dutch legislation, as described in [1.4](#), the BPRC and the NIN have been increasingly replacing, reducing and refining NHP research. For example, more use is being made of cell culture techniques, eliminating the need to obtain certain information by studying primates. The BPRC also undertakes ethological research (observation and training) as a basis for refinement – through the work, behavioural researchers improve the primates' living conditions and animal trainers seek to minimise the stress that the animals experience. Animal handlers, for example, no longer have to forcefully hold laboratory animals to give an injection thanks to training – the animals offer a foot or leg of their own accord in return for rewards. Great strides have also been made in the social and experimental accommodation of the primates, and behavioural scientists are working on the composition of the social groups.

All NHP researchers are expected to follow the 3R principles. Licence applications are reviewed by the DEC and the CCD for compliance with the principles. However, the 3R approach is fundamentally

limited insofar as the animal experiment is its starting point.¹⁵² An alternative approach was proposed by the NCad in 2016, under which the starting point would be to consider what questions researchers in a particular discipline are seeking to answer, and what – preferably animal-free – research methods could be used to address those questions. Thus, the questions to be addressed would form the basis for a roadmap to animal-free research within a discipline.¹⁵³ What knowledge do we want to have, say, ten years from now, and how can we obtain it without using NHPs? Instead of the existing focus on the 3R approach, researchers should focus on the research questions of their field in the broadest sense. That would require a new way of thinking and a corresponding culture change – a paradigm shift.¹⁵⁴

The roadmap-based approach is consistent with a broader shift in the Netherlands towards a greater focus on the development of animal-free innovations. The TPI Programme plays an important role in that context.¹⁵⁵ The TPI Programme supports Dutch policy ambitions regarding the promotion of animal-free innovations and the phasing out of animal research. Under the guidance of the Ministry of LNVN (formerly LNV), various stakeholders are collaborating on projects aimed at reducing animal research. In 2020, it was decided to extend and intensify the TPI Programme. In addition, the National Growth Fund invested €124.5 million in 2024 in the CABT with the aim of driving the transition to animal-free innovation. The funding supports research projects and initiatives aimed at developing animal-free alternative methods. The money also pays for education and training on NAMs and their implementation.¹⁵⁶ In its evaluation of the roadmap approach, the NCad notes 'that with the roadmaps towards animal-free research, a good model has been established to identify opportunities within basic scientific research areas. The roadmaps also portray the challenge of balancing ambitious and groundbreaking goals with the need for a passable pathway with concrete intermediate goals, along which the field can move forward.'¹⁵⁷ However, the NCad also notes that the wider community has not so far been adequately involved in drafting roadmaps, if at all. Furthermore, not enough has been done to develop a vision for detailing and implementing the roadmaps. In the future, more attention should be paid to societal and ethical aspects, to clear ownership of the various sub-goals, to increasing the resources allocated to achieving the defined sub-goals, and to progress monitoring. In relation to NHP research, the existing roadmaps for the neurosciences and immunology are important.¹⁵⁸ The development of a similar roadmap for infectious disease research is also desirable.

¹⁵² Grimm et al., 'Advancing the 3Rs'. Grimm et al.

¹⁵³ NCad, 'Transitie naar proefdiervrij onderzoek – Over mogelijkheden voor het uitfaseren van dierproeven en het stimuleren van proefdiervrije innovatie' ['Transition to animal-free research – About the scope for phasing out animal research and promoting animal-free innovation'].

¹⁵⁴ As Thomas Kuhn has demonstrated, a certain degree of conservatism in science within an existing paradigm is normal and even desirable. When the number of problems within a paradigm increases and an alternative paradigm becomes available, a paradigm shift occurs. Formulating research questions and designing studies in a different way, guided by a roadmap for animal-free research and resulting in a substantial reduction in the number of animal experiments, constitutes such a paradigm shift. Kuhn, *The structure of scientific revolutions*. For an example from the field of animal research that illustrates a degree of conservatism among researchers, see: Veening-Griffioen et al., 'Tradition, Not Science, Is the Basis of Animal Model Selection in Translational and Applied Research'.

¹⁵⁵ TPI, 'Voortgangsrapportage 2022 programma Transitie Proefdiervrije Innovatie' ['Animal-free Innovation Transition Programme Progress Report 2022'].

¹⁵⁶ Universiteit Utrecht, 'Nationaal Groeifonds investeert 124,5 miljoen euro in transitie naar proefdiervrije innovatie' ['National Growth Fund invests €124.5 million in transition to animal-free innovation'].

¹⁵⁷ NCad, 'Evaluatie van het NCad advies "Transitie naar proefdiervrij onderzoek"' [Evaluation of the NCad report "Transition to animal-free research"].

¹⁵⁸ KNAW, 'Excellent hersenonderzoek met minder dierproeven. Kansen en uitdagingen voor proefdiervrij onderzoek in de neurowetenschappen' ['Excellent brain research with fewer animal experiments. Opportunities and challenges for animal-free research in the neurosciences']. NCad, 'Streefbeeld voor proefdiervrije innovaties in de immunologie' ['Roadmap for animal-free innovation in immunology'].

In the context of Dutch transition policy, numerous organisations are actively working to develop and promote animal-free alternatives. The organisations in question work with scientific institutions, regulatory bodies and the private sector to promote and implement such alternatives. Examples include the Dutch Society for the Replacement of Animal Testing (Stichting Proefdiervrij), People for the Ethical Treatment of Animals (PETA) and the European Partnership for Alternative Approaches to Animal Testing (EPAA). Those organisations play an important role in raising awareness of the benefits of alternatives to animal research. They encourage the scientific community to embrace animal-free methods and support the transition to innovative, ethically sound research practices.

Much could be gained by fostering a closer relationship between animal-free innovation on the one hand and NHP research on the other. Those often remain separate worlds, which do not know how to connect with each other (or how to avoid sometimes getting in each other's way), although each could benefit from contact with the other. Familiarity with the relevant methods within the research community would improve decision-making when choices must be made between NAMs and NHP research, based on a better understanding of the strengths and weaknesses of the various options. Insights gained from NHP research are highly relevant to researchers engaged in the development of alternatives. For example, cystic fibrosis research carried out using human intestinal organoids has recently yielded valuable results¹⁵⁹, but the disease is also being investigated using NHPs.¹⁶⁰ Better cooperation can lead to a reduction in NHP experiments, as existing knowledge is better utilised.

Where the BPRC is concerned, closer relations with research institutes and universities would lead to greater interaction with NAM researchers. The BPRC could provide the NAM field with NHP data, especially where the alternatives under investigation are based on NHP (stem) cells or tissues. Conversely, NAM researchers could reinforce the BPRC's own work on NAMs.

3.4 International importance of Dutch NHP research

Having looked at the numbers and the research areas addressed by NHP research in the Netherlands, it is important to also assess the scientific value of that research in an international context. The BPRC itself publishes annual data on the number of publications and their average impact factor.¹⁶¹¹⁶² The NIN also monitors publication numbers.¹⁶³ Our analysis of the international literature shows that the Netherlands is an important NHP research nation. The Netherlands ranks eighth in terms of the volume of NHP research carried out, as measured by the number of publications. The Netherlands is a major contributor to NHP research within the EU. For example, the Netherlands was involved in 64 per cent of published primate research in the EU in 2021 (see [figure 7](#)). The Netherlands' highest annual contribution to global NHP research was 2.6 per cent in 2021 (see [figure 6](#)).

¹⁵⁹ Bierlaagh et al., 'Repeatability and Reproducibility of the Forskolin-Induced Swelling (FIS) Assay on Intestinal Organoids from People with Cystic Fibrosis'.

¹⁶⁰ Farrow et al., 'Towards Human Translation of Lentiviral Airway Gene Delivery for Cystic Fibrosis'.

¹⁶¹ The impact factor is a measure that reflects how often a scientific journal is cited. An article published in a journal with a higher impact factor is expected to be read more often.

¹⁶² BPRC, 'BPRC's onderzoeksresultaten - De bijdrage van ons onderzoek aan de vooruitgang in de medische wetenschap' ['The BPRC's research results - The contribution of our research to the advancement of medical science'].

¹⁶³ NIN, 'Roelfsema Group - Visual perception, blindness & plasticity'.

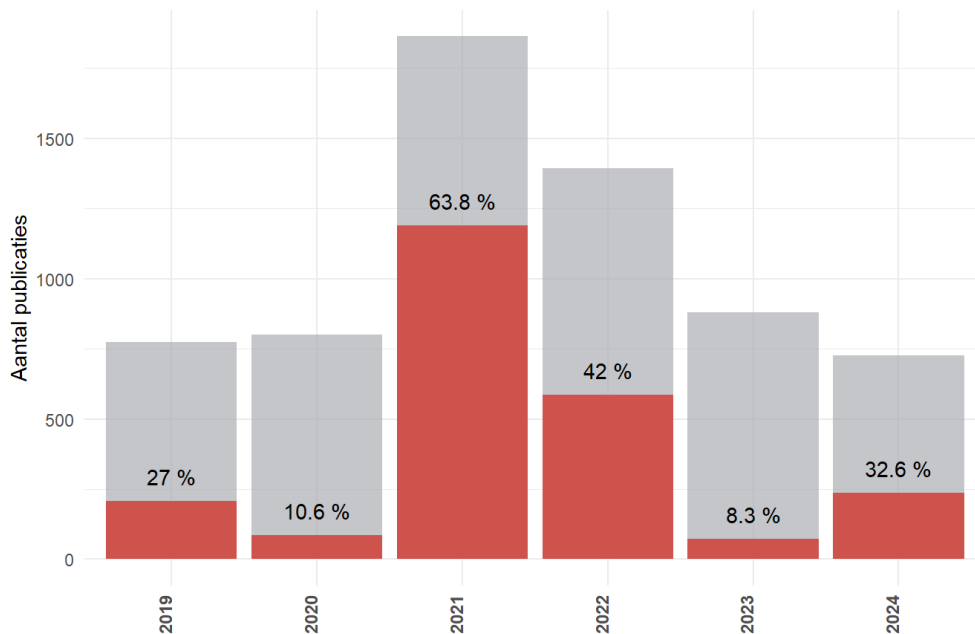


Figure 7 Overview of the number of publications with NHPs per year in the EU and the Netherlands since 2019

The Netherlands is also among the ten countries undertaking the most basic research in the last six years (including 2024). The Netherlands also contributed significantly to the SARS-CoV-2 research.

Besides the scientific value of the research, it is also important to consider the geopolitical aspects of NHP research in the Netherlands in an international context. The Netherlands is home to one of nearly twenty primate centres around the world that are public entities, breed their own laboratory animals and have their own research programmes (see 3.1). The largest concentration of primate centres is in the United States. Europe has a limited number of such primate centres. There are primate centres in Germany, France and the UK, as well as in the Netherlands.¹⁶⁴

As explained in section 2.3, the global supply of primates for research is decreasing. Reports from the United States and the European Union show that demand for NHPs for research is high, while supply is falling. After the SARS-CoV-2 pandemic, this situation was exacerbated by the cessation of primate exports from China and by other supply problems. The shortage of primates coming from Southeast Asia and Mauritius, combined with the ban on importing wild primates to the EU, makes finding solutions difficult. The desire to use only NHPs from self-sustaining colonies within the EU is not realistic in the short term.¹⁶⁵ Countries outside Europe are investing to achieve self-sufficiency in NHP research by building new primate centres.¹⁶⁶ Although Dutch NHP researchers often collaborate in international consortia, and sometimes conduct NHP experiments abroad, the existence of the BPRC provides the Netherlands with a degree of self-sufficiency in NHP research.

The welfare standards at NHP facilities are generally higher in many European countries than in other parts of the world. The discrepancy is due to various factors, including differences in legislation, practices, awareness of the welfare needs of NHPs and the health status of animals. Countries

¹⁶⁴ BPRC, 'Ambitieplan BPRC - voor de periode 2019-2025' ['BPRC ambition plan for the period 2019 to 2025'].

¹⁶⁵ Grimm et al., 'Advancing the 3Rs'. Anderson, David and McCall, Kathy, 'Feasibility Study under Article 10 of Directive 2010/63/EU on Sourcing Non- Human Primates Only from Self-Sustaining Colonies'. Kemnitz et al. (2008), *Animal Research in a Global Environment*.

¹⁶⁶ Normile, Dennis, 'China Bets Big on Brain Research with Massive Cash Infusion and Openness to Monkey Studies'. Oliver Milman, 'Plan for US "mini-city" of 30,000 monkeys for medical research faces backlash'.

outside Europe also recognise the importance of animal welfare and have guidelines for improving the care of NHPs. Some form of ethical review is required for NHP research projects everywhere. However, there are differences in the way guidelines on matters such as animal accommodation are implemented and enforced. In general, EU directives are the most detailed and strict, while countries like the United States, China and Japan show more variability in implementation and enforcement.¹⁶⁷ For example, the age-related minimum cage and space requirements for primates under the European directive are greater than those stipulated in the US guidelines.¹⁶⁸ Also, it is more common for NHPs to be housed in pairs or groups in Europe than in the United States or Asia. If all NHP research took place outside Europe, it would likely lead to a net decrease in animal welfare and, consequently, in the quality of research.

¹⁶⁷ Chatfield and Morton, 'The Use of Non-human Primates in Research'. SCHEER, *Final Opinion on the Need for Non-Human Primates in Biomedical Research, Production and Testing of Products and Devices (Update 2017)*. Bayne, Hau and Morris, 'The Welfare Impact of Regulations, Policies, Guidelines, and Directives and Nonhuman Primate Welfare'.

¹⁶⁸ Coleman et al., 'Common Husbandry, Housing, and Animal Care Practices'.

4 New approach methodologies

The emergence of research methods based on the use of human tissue, stem cells, cell culture systems, computer models and data analysis has increased the range of methodological options for investigating the effects of treatments. Such so-called 'new approach methodologies' (NAMs) vary in terms of the underlying technologies, their maturity and their areas of application.¹⁶⁹ In 2016, the European Chemicals Agency (ECHA) introduced the term NAM for methods such as *in silico* approaches and *in vitro* experiments.¹⁷⁰ NAMs are not only being developed to replace animal experiments, but can also independently contribute to the understanding of human disease mechanisms and the effects of chemical substances on human cells and tissues.

Research with NHPs has a long scientific tradition. Although research with human subjects is sometimes preferred, early-stage research on humans carries risks and often takes place in less controlled environments than animal research, making it more difficult to accurately measure and interpret effects. Animal research, and in particular research with NHPs, are therefore used in the early stages of research into the effectiveness and side-effects of treatments. However, researchers also recognise the limitations of research with NHPs.¹⁷¹ NAMs can serve as alternatives to animal experiments, but many NAMs have yet to be shown to provide sufficient clarity regarding effects to make them suitable for certain applications, either on their own or in combination with other research methods. In this chapter, the committee discusses the NAMs that researchers can use for research purposes similar to those for which NHP research is used, and considers the contribution that NAMs can make to the phasing out of NHP experiments.

Controlled Human Infection Models (CHIMs) are not usually classified under NAMs but should be mentioned here.¹⁷² In such studies, healthy people are infected with, for example, malaria so that malaria vaccines can be tested. The use of CHIMs for vaccine testing is possible only in connection with diseases against which good medicines are available.

NAMs, CHIMs and other cutting-edge research directly on humans can together facilitate a transition to a scientific research landscape where fewer NHPs are used, or possibly none at all. However, it is important to remember that such societal transitions require multi-actor and multi-issue engagement. That implies investing not only in the 'scientific-technical' research on alternatives, but also in defining new roles, values and responsibilities for various actors, including researchers, regulatory bodies, research funding providers, journals, patients and citizens. What is needed for the public to accept vaccines that have not been tested on NHPs? How can research funding providers, journals and regulatory bodies be encouraged to accept the evidential value of non-animal models more often than they already do?

¹⁶⁹ Previously, 'NAM' was also used as an abbreviation of 'non-animal model'. The committee follows the broader definition of 'new approach methodology' because some NAMs do involve the use of some form of animal material.

¹⁷⁰ European Chemicals Agency, *New Approach Methodologies in Regulatory Science*.

¹⁷¹ RIVM, 'Landscape New Approach Methodologies (NAMs) safety assessment pharmaceutical products'.

¹⁷² Sauerwein, Roestenberg and Moorthy, 'Experimental Human Challenge Infections Can Accelerate Clinical Malaria Vaccine Development'. Roozen et al., 'Single Immunization with Genetically Attenuated PfΔmei2 (GA2) Parasites by Mosquito Bite in Controlled Human Malaria Infection'. Bijker, Sauerwein and Bijker, 'Controlled Human Malaria Infection Trials'. Rid and Roestenberg, 'Judging the Social Value of Controlled Human Infection Studies'. Shah et al., 'Ethics of Controlled Human Infection to Address COVID-19'.

4.1 Relationship between NAMs and NHP experiments

There are various ways in which NAMs could serve as alternatives to research on NHPs. The NAMs in question all have their own particular limitations, which the committee identifies below. One advantage of NAMs is that they can shed light on the effects and risks of a treatment, thus providing confidence that the treatment can be tested directly on humans, without having to first conduct experiments with NHPs.¹⁷³ A second advantage is that, in some cases, NAMs can provide as much or even greater insight into the effects and risks of treatments than experiments with NHPs.¹⁷⁴ Thirdly, in situations where animal testing is still necessary, NAMs can support decision-making regarding the most appropriate animal model to use. Finally, because NAMs often involve single-organ models, they can provide more precise information about a treatment, allowing the researcher to define the research question more precisely or to improve the treatment before proceeding to test it on NHPs or humans. That in turn can mean less suffering for the NHPs used in research, or to the use of fewer NHPs. However, the extent to which NAMs can actually replace NHP research depends to a considerable extent on the particular research fields and the precise research questions involved. It is partly for that reason that the roadmap-based approach described above, in which the starting point for decision-making is not the NHP experiment but the underlying research question, is so important.

Furthermore, NHPs can play a role in the transition to animal-free research. The reason being that whether NAMs can reliably and predictably replace NHP research depends partly on the ability to compare the new situation (characterised by NAMs use) with the old situation (characterised by NHP use).

The range of NAMs that are emerging is both large and diverse. Strictly speaking, systematic literature review is not an NAM, but the committee believes it should be mentioned in this context because a systematic review can yield information showing that an animal study is not necessary or desirable, in light of earlier research results.¹⁷⁵

4.2 Main groups of NAMs

In this section, NAMs are described on the basis of division into two groups: those based on *in vitro* methods (organ or tissue-like models outside the body) and those based on *in silico* methods (the computerised analysis of existing data). NAMs will very often be used in combinations. For example, *in vitro* research methods may be used in combination with clinical trials and *in silico* analyses.

In vitro methods

An *in vitro* method involves cell structures or tissue structures taken from a (human or animal) donor being kept alive outside the body in specially developed culture media. The cultured material may take the form of organoids (where adult stem cells or induced pluripotent stem cells (iPSC) form simplified tissues resembling parts of organs such as the intestine, lung or liver¹⁷⁶), organs-on-chips (where a synthetic 'chip', with small channels for fluids, contains organ or cell tissue and sensors to measure certain functions of that tissue¹⁷⁷) or *ex vivo* tissue cultures (tissues, often in thin slices, that

¹⁷³ See, for example, with regard to the infection of an airway epithelial cell model with tuberculosis: Barclay et al., 'Airway epithelial cells mount an early response to mycobacterial infection'.

¹⁷⁴ Eichmüller and Knoblich, 'Human Cerebral Organoids—a New Tool for Clinical Neurology Research'; Menon, Muglia and Levin, 'Review on new approach methods to gain insight into the fetomaternal interface physiology'.

¹⁷⁵ Ritskes-Hoitinga et al., 'Systematic Reviews of Preclinical Animal Studies Can Make Significant Contributions to Health Care and More Transparent Translational Medicine'. NCad, 'Handreiking Synthesis of Evidence in proefdieronderzoek' [Guidebook Synthesis of Evidence in Animal Research].

¹⁷⁶ RIVM, 'Landscape New Approach Methodologies (NAMs) safety assessment pharmaceutical products'.

¹⁷⁷ Ingber, 'Human Organs-on-Chips for Disease Modelling, Drug Development and Personalized Medicine'.

come directly from donor organs). Many of the techniques in question utilise the ability of stem cells to develop into cells of certain types, resulting in a model whose characteristics are determined by the genetic makeup of the patient or donor.¹⁷⁸ Hence, simple or more complex models can be created, which resemble the human liver, skin, kidney, etc. Using such techniques, it is possible to study the effects of a treatment on patient-specific cells. NAMs of this type provide models that originate directly from or closely resemble the patient who will ultimately undergo the treatment. The effects of a treatment can therefore be determined quite accurately, sometimes for a larger group of patients and sometimes for specific patients. This is an example of 'personalised medicine'.¹⁷⁹ It should be noted, however, that NHP research or other animal research may still be needed to validate resulting treatment. Such models can also be used to determine the toxic effects of chemicals or environmental factors.¹⁸⁰ Techniques for studying toxic effects on the heart and liver have reached a particularly advanced stage of development. NHPs are not used for toxicity research in the Netherlands.

The various *in vitro* methods are all at different stages of development and have their own limitations and challenges. At the time of writing (2024), many of the methods are in the process of being standardised and qualified for use in certain situations.¹⁸¹ Until that final stage of development has been completed, the pharmaceutical industry and regulators cannot proceed with implementation. The Netherlands is a leader in research with organoids and organs-on-chips.¹⁸² According to the roadmap towards animal-free brain research, it is likely that, within five to ten years, it will be possible to develop additional brain cell types and more complex brain models (not only organoid models, but also 'assembloid' models) for *in vitro* brain research.¹⁸³ At the moment, techniques such as organoid-based modelling are used mainly for studying the potential of possible treatments for particular diseases, for preclinical disease research and for designing a *toolkit* for future transplants.¹⁸⁴

Little research is yet being done into the use of NAMs based on cells and tissues obtained from NHPs. If the same effects can be observed in NHP organoids (or directly in human organoids) as in NHPs themselves, that could lead to fewer NHP experiments being performed.¹⁸⁵ Hence, the database of past NHP research results could be used to qualify NAMs for certain purposes. For example, the industry is already using data from mouse experiments to qualify NAMs based on mouse tissues and stem cells.¹⁸⁶ That is the case only if the same pathogen is involved, not in situations that involve

¹⁷⁸ Mijnders, Fuchs and Nieuwenhuis, 'Mogelijke toepassingen van organoïden in de geneeskunde' ['Possible applications of organoids in medicine].

¹⁷⁹ Leung et al., 'A Guide to the Organ-on-a-Chip'.

¹⁸⁰ Much of the toxicity research undertaken adheres to OECD guidelines: OECD, 'Guidelines for the Testing of Chemicals'.

¹⁸¹ Whereas the terms 'validation' and 'acceptance' are used in relation to the introduction of NAMs for the testing of chemicals, the preference is for the terms 'qualification' and 'admission' when referring to NAMs for pharmaceutical products. The qualification of NAMs for pharmaceutical applications mainly involves establishing that NAMs are fit for purpose in a particular usage scenario. The committee therefore refers to the 'qualification' of NAMs, rather than the 'validation' of NAMs. See RIVM, 'Towards the Future of Toxicity Testing. Landscape New Approach Methodologies (NAMs) Safety Assessment Pharmaceutical Products'. RIVM, 'Landscape New Approach Methodologies (NAMs) Safety Assessment Chemical Substances'. Regarding the EMA's role in that context, see also: EMA, 'Ethical Use of Animals in Medicine Testing'.

¹⁸² Shoji et al., 'Global Meta-Analysis of Organoid and Organ-on-Chip Research'. Shoji et al..

¹⁸³ KNAW, 'Excellent hersenonderzoek met minder dierproeven. Kansen en uitdagingen voor proefdiervrij onderzoek in de neurowetenschappen' ['Excellent brain research with fewer animal experiments. Opportunities and challenges for animal-free research in the neurosciences']. See also the recent work: Onesto, Kim and Pasca, 'Assembloid models of cell-cell interaction to study tissue and disease biology'.

¹⁸⁴ Miura et al., 'Engineering Brain Assembloids to Interrogate Human Neural Circuits'; Shoji et al., 'Global Meta-Analysis of Organoid and Organ-on-Chip Research'. Ewart et al., 'Performance Assessment and Economic Analysis of a Human Liver-Chip for Predictive Toxicology'.

¹⁸⁵ See, for example, Kawasaki et al., 'Farm and Companion Animal Organoid Models in Translational Research'. Ganesh et al., 'A Rectal Cancer Organoid Platform to Study Individual Responses to Chemoradiation'.

¹⁸⁶ Kang et al., 'Complex in vitro models positioned for impact to drug testing in pharma'.

novel or poorly understood diseases. Furthermore, all models will ultimately have to be qualified for human use contexts.

In vitro methods also have limitations. First, researchers often obtain the tissues or cells from living organisms. Using, reproducing and maintaining tissues outside the body of a human or animal is complicated – some cells lose some of their functions under such circumstances. As a result, many models are lost during the course of the research, or the insight gained relates only to a short period of exposure to the treatment. Moreover, it remains difficult to link an *in vitro* model of one organ to effects in other organs, or to natural barriers such as the blood-brain barrier, or to the systemic effects of, for example, metabolites of medicines in different parts of the body. Significant progress is already being made in various studies.¹⁸⁷ Despite considerable progress in the development of linked organ models, the incomplete nature of current scientific understanding of kinetics and metabolism has prevented NAM developers from constructing a complete organ or human model, such as a model of the immune system, which incorporates all relevant functions.¹⁸⁸

Moreover, NAM research that involves the use of donated human tissue material is subject to legal constraints, because there may be doubt as to whether the donor has given full consent for the particular use.¹⁸⁹ In that context, there is also debate concerning the right to withdraw consent, which makes it difficult to keep NAMs based on human tissues and cells available for an extended period of time. The Body Material Control Bill, which is still undergoing preparation, proposes the application of even stricter restrictions in that field.¹⁹⁰

Finally, there are still clear limits to the use of *in vitro* methods in NAMs research. Experiments with NAMs should be reproducible, like all scientific experiments.¹⁹¹ Achieving that is difficult, because the reproducibility of biomedical research in general is currently threatened by factors such as lack of transparency and access to data. The investigated effects must be measurable within the NAM model, and it must be possible to examine the tissues for longer periods of time to be sure about the (lasting) effect of a response and the occurrence of any side-effects. The standardisation of organ-on-chip models and the validation of quantitative measurements against measurements in humans are still in progress.¹⁹² Additional resources should be made available for such standardisation; public-private partnerships are a good vehicle for standardisation research.

The potential value of NAMs for use in preparation for clinical trials is illustrated by, for instance, the fallout from trials in which unexpected effects are observed in humans. For example, the first in-human trial with BIA 10-2474 led to the death of a subject, while a trial with TGN1412 led to an unexpected cytokine storm in humans, even though the medicines in question had been extensively tested in mice and NHPs.¹⁹³ It was subsequently discovered that BIA 10-2474 was fatal to human neurons *in vitro* due to aspecific target bonding, while *in vitro* experiments with human blood cells

¹⁸⁷ See, for example: Ronaldson-Bouchard et al., 'A Multi-Organ Chip with Matured Tissue Niches Linked by Vascular Flow'. Picollet-D'hahan et al., 'Multiorgan-on-a-Chip'. Vasconez Martinez, Frauenlob and Rothbauer, 'An Update on Microfluidic Multi-Organ-on-a-Chip Systems for Reproducing Drug Pharmacokinetics'. Sasserath et al., 'Differential Monocyte Actuation in a Three-Organ Functional Innate Immune System-on-a-Chip'.

¹⁸⁸ Kim et al., 'Recent Development of Brain Organoids for Biomedical Application'.

¹⁸⁹ NCad, 'De beschikbaarheid en toegankelijkheid van menselijk weefsel voor biomedisch onderzoek en onderwijs' [The availability and accessibility of human tissue for biomedical research and education]. Regarding organoids, see De Jongh et al., 'Organoids'.

¹⁹⁰ Minister of VWS, Wetsvoorstel zeggenschap lichaamsmateriaal [Body Material Control Bill]. Explanatory Memorandum.

¹⁹¹ Collins and Tabak, 'NIH plans to enhance reproducibility'.

¹⁹² Nahon et al., 'Standardizing Designed and Emergent Quantitative Features in Microphysiological Systems'.

¹⁹³ Kaur et al., 'TGN-1412 and BIA-2474 Trials with Tragic End'.

revealed important response differences between NHPs and humans.¹⁹⁴ Although such cases support the inclusion of human *in vitro* data in pre-clinical research, they do not demonstrate that the use of such data could eliminate the need for NHP research in preparation for clinical trials.

In due course, *in vitro* NAMs could be used to address some of the research questions that need to be answered in the phase between laboratory research and clinical trials, without the need to carry out NHP experiments as an intermediate step.¹⁹⁵ It should be noted, however, that, as developing NAMs acquire more and more of the characteristics of human models, new ethical questions may arise, as is already the case with the application of human brain organoids.¹⁹⁶

In silico methods

A second group of NAMs uses computers and artificial intelligence (AI) to process existing information in novel ways, leading to new insights. These are referred to as *in silico* methods. *In silico* methods often use predictive mathematical models and, like the other NAMs, are often used in combination with other similar methods and with methods of other kinds. Such approaches provide researchers with estimates of the probability of the uptake, dispersal, metabolism, excretion and biological effects of substances.¹⁹⁷ One example is a computer model that uses AI for the automated analysis of datasets to identify parameters that can predict the effect of a treatment. Another example is the use of 'big data' analysis methods to combine existing datasets from different studies, and thus obtain new insights. Such insights therefore depend not only on the quality of computers and software, but also on the availability, quality and relevance of the underlying data sources.

The use of *in silico* NAMs is valuable mainly for obtaining pointers at an early stage as to the direction that further research should take. Used in that way, NAMs can also help to improve the design of experiments. In particular, *in silico* NAMs play a role in accelerating the exploratory phase of research, when researchers try to gain insight into the relevant parameters. Hence, NAMs of this kind have the potential to replace animal experiments in the early, exploratory stages of research. Although some of the replaced animal research may involve NHPs, the complexity of the experiments in question is such that the NAMs will more often contribute to replacement of the animal testing that takes place earlier in the research process.¹⁹⁸ There is also evidence that *in silico* models can, in some cases, predict effects in humans better than animal models.¹⁹⁹

4.3 Use of NAMs to replace NHP research

Because an animal experiment and a NAM never measure exactly the same thing, NAMs cannot replace animal experiments on a one-to-one basis. The choice of method should be led by the research question, and the best alternative to animal research will often be a combination of NAMs. That research question, or problem definition, should therefore be the starting point for the development and implementation of NAMs.²⁰⁰ The 'context of use' is of particular importance here: "*a full, clear and concise description of the way a novel methodology is to be used and the medicine*

¹⁹⁴ van Esbroeck et al., 'Activity-Based Protein Profiling Reveals off-Target Proteins of the FAAH Inhibitor BIA 10-2474'. Eastwood et al., 'Monoclonal antibody TGN1412 trial failure explained by species differences in CD28 expression on CD4+ effector memory T-cells'.

¹⁹⁵ Shoji et al., 'Global Meta-Analysis of Organoid and Organ-on-Chip Research'.

¹⁹⁶ See, for example, Hoppe et al., 'Human Brain Organoid Code of Conduct'.

¹⁹⁷ Madden et al., 'A Review of *In Silico* Tools as Alternatives to Animal Testing'.

¹⁹⁸ Portugal-Cohen et al., 'Exploitation of alternative skin models from academia to industry'.

¹⁹⁹ Passini et al., 'Human In Silico Drug Trials Demonstrate Higher Accuracy than Animal Models in Predicting Clinical Pro-Arrhythmic Cardiotoxicity'.

²⁰⁰ RIVM, 'Infectieziektenbestrijding' ['Infectious disease control'].

*development related purpose of the use.*²⁰¹ The context of use may be relatively generic (children up to twelve years old) or much more specific (people with a particular genetic trait).

For example, human stem cell technology makes it possible to include genetic variations between people in NAM-based laboratory research. That enables the development of personalised models that better simulate the effects of substances in people of different genetic backgrounds, both for disease modelling and for medicine development.

AI researchers are able to rapidly analyse large amounts of data and predict the likelihood of experiments being applicable. That reduces the need for animal experiments because, with such AI support, *in vitro* and *in silico* models are increasingly able to predict human responses to particular treatments.²⁰² For the study of monogenetic diseases, such as cystic fibrosis, organoids are actually better models than animals, because of the genetic heterogeneity of CFTR mutations in the gene that codes the cystic fibrosis transmembrane conductance regulator (CFTR).²⁰³

While such advances are promising and are sometimes removing the need for NHP experiments, many researchers believe that NAMs cannot yet completely replace animal research.²⁰⁴ Traditionally, NAMs have mainly provided insight into the effects on molecules, genes, cells or proteins, and provided pointers as to the possible effects in the ultimate target group. However, a full understanding of how the results translate to patients usually requires *in vivo* trials as well.²⁰⁵ Such *in vivo* trials offer insight into the effects over longer periods of time, in different types of patient, and into interactions with other body systems such as the immune system. Consider, for example, the liver, which plays an important role in the metabolism of many substances into usable or, indeed, toxic products: while sophisticated liver organoids do already exist, the excretion of substances or their accumulation in certain organs can still be measured only *in vivo*. However, pharmacokinetic or biokinetic computer models can sometimes also be used successfully in that context to predict *in vivo* concentrations of test substances and their metabolites in organ systems.²⁰⁶ Such models leverage knowledge regarding the anatomy and physiology of an organism, combined with knowledge regarding the physical-chemical properties of a substance to predict changes in the concentrations in the various organs.²⁰⁷

The statistical power of experiments also plays an important role. When, for example, materials from different donors are used in stem cell research, it is essential to have enough subjects and to perform enough measurements to achieve the necessary statistical power. Consequently, if the size of a study is limited for cost reasons, or if some subjects withdraw, its statistical power may be compromised.²⁰⁸ The statistical power of an NHP study can also be compromised sometimes by the use of a very small number of primates. In many cases, therefore, NHP research is *underpowered*.²⁰⁹ The size of the sample required for a model to have sufficient statistical power depends on the research question and the context of use.²¹⁰

²⁰¹ EMA, 'Essential considerations for successful qualification of novel methodologies'.

²⁰² Corradi et al., 'The Application of Natural Language Processing for the Extraction of Mechanistic Information in Toxicology'.

²⁰³ Chen et al., 'Pharmacological analysis of CFTR variants of cystic fibrosis using stem cell-derived organoids'.

²⁰⁴ Burm et al., 'Alternative Methods for the Use of Non-Human Primates in Biomedical Research'.

²⁰⁵ Schmeisser et al., 'New Approach Methodologies in Human Regulatory Toxicology – Not If, but How and When!'; Daniel, 'Extracorporeal perfusion of isolated organs of large animals – Bridging the gap between *in vitro* and *in vivo* studies'.

²⁰⁶ Combes et al., 'Early Predictors for Infection Recurrence and Death in Patients with Ventilator-Associated Pneumonia'.

²⁰⁷ Blauboer, 'Biokinetic Modeling and *in Vitro*-*in Vivo* Extrapolations'.

²⁰⁸ Brunner et al., 'Power and Optimal Study Design in iPSC-Based Brain Disease Modelling'.

²⁰⁹ Bliss-Moreau et al., 'Improving Rigor and Reproducibility in Nonhuman Primate Research'.

²¹⁰ Huber et al., 'Strength of Nonhuman Primate Studies of Developmental Programming'.

NAMs could actually drive up the number of animal experiments by answering research questions more quickly and precisely, accelerating the flow of candidate medicines, which, under current EMA guidelines, would then need to be qualified for relevant contexts of use by means of animal research. Also, animal material is sometimes required for the use of certain NAMs.

The reduction and replacement of animal research in general, and NHP research in particular, is the focus of considerable attention from regulatory bodies as well. A writing group is active within the EMA to consider where NHPs are still required for medicine development, what scope the current international guidelines allow for reducing the use of NHPs (in terms of the numbers involved, the amount of discomfort experienced and possible complete replacement), and what scope there is for the targeted use of NAMs within the wider framework in order to minimise NHP use. To that end, talks are being held with various consortia from the medical and pharmaceutical industries to catalogue all the alternatives to NHP research. The EMA will make recommendations to the pharmaceutical industry on what needs to be done to assess whether an NAM is an adequate replacement for NHP research. The EMA was prompted to address this subject by the global shortage of NHPs during the SARS-CoV-2 crisis. The FDA then published a position paper on the use of NHPs, citing relevant ICH guidelines.²¹¹ The EMA wants to catalogue NAMs so that smaller pharmaceutical companies are less likely to simply assume that NHP research is the most appropriate solution, but would also consider EMA-supported alternatives. A good example of such an NAM is the recently developed lymphoid organ-on-a-chip, which can be used to model mRNA vaccine booster strategies.²¹² The preliminary report is likely to be published on the EMA website for public consultation in the course of 2025; the NHP Research Committee did not have access to draft versions of the report.

In general, the EMA and the CBG encourage NAM researchers to contact the regulatory bodies as early in the development of their methods as possible. That way, the entire NAM development and implementation process can begin from a clear understanding of the problem addressed, the purpose that the NAM should fit, and the context of use.

The diversity of NAMs and the wide range of associated research questions and contexts of use make it difficult to directly compare NAM use with NHP research. However, researchers do believe that promising NAMs could partly, or even to a large extent, replace NHP research in the short or longer term (see also [Table 4](#)). By comparison with many NAMs, NHP experiments have significant limitations in terms of their qualification for human-relevant contexts of use. Comparability with the ultimate target group often still has to be established by means of clinical trials. At the moment, however, NAMs are not yet able to address all the research questions for which NHP is considered necessary. With both NAMs and NHP research, translatability and statistical power can be problematic, but NAMs are better for predicting responses at the molecular and cellular levels. Nevertheless, despite all the recent progress in building (parts of) organs *in vitro*, NAMs are often still lacking in terms of their ability to simulate the complexity of an entire organ system or organism over long periods of time.

Another way to potentially reduce NHP research is to improve international coordination and knowledge sharing. More international cooperation could prevent unnecessary duplication and

²¹¹ Brown and Wange, 'Considerations Regarding the Use of Nonhuman Primates in Assessing Safety Endpoints for Pharmaceuticals'.

²¹² Jeger-Madiot et al., 'Modeling memory B cell responses in a lymphoid organ-chip to evaluate mRNA vaccine boosting'.

therefore reduce the amount of NHP research carried out. Unnecessary duplication could also be prevented by the preregistration of NHP experiments.²¹³ Other actors in the scientific process, such as journals and research funding bodies, could play a stimulating and facilitating role in this context. As part of the TPI Programme, Helpathons are organised for that purpose, where scientists help each other answer scientific and societal questions by, for example, identifying suitable NAMs.²¹⁴ Knowledge sharing is also facilitated by a wide-spectrum approach to research, where profiles of particular patient groups are used to investigate the effect of a treatment in multiple diseases. In addition, treatments for particular pathologies could be adapted to make them suitable for use by patients with related conditions.²¹⁵ That way, any NHP research that is undertaken can make a wider contribution to scientific knowledge development.

From its discussions with NAM researchers, the committee learnt that significant NAM developments are anticipated in the near future, but also that NHP research is expected to remain necessary for the time being.

4.4 Industry's role in using NHPs and the search for alternatives

In the Netherlands, the biomedical and pharmaceutical industries do not conduct independent research using NHPs. However, they may commission the BPRC to carry out such research for them, or they may carry out research abroad. In line with its remit, the committee did not investigate the extent to which those industries are engaged in research using animals other than NHPs. Nevertheless, it is clear that animal research is performed to progress research from the laboratory to the clinic.

Furthermore, industry players in the Netherlands and Europe are actively involved in research on NAMs in partnership with universities and other public research centres.²¹⁶ Until relevant NAMs – that is, appropriate for the intended user context – have been qualified and accepted by the EMA, companies will not use them instead of animal models, because that would imply an unacceptable risk of their product not being licensed.²¹⁷ Greater cooperation amongst industry players would make NAM research less fragmented, but competitive considerations are liable to hinder such cooperation. However, the issue of industry and the authorities holding each other back (see section 1.5.4) continues to hamper efforts to accelerate progress and securing tangible results. A lot could be achieved – in terms of breaking the deadlock and identifying alternatives to NHP research – by researchers working closely with the staff at the EMA, CBG and CCD, and especially by engaging with those bodies at an early stage. For example, a manufacturer could use the 'weight-of-evidence' approach, based on results obtained using a combination of research methods (e.g. previous animal research, research with human subjects and *in vitro* research), to argue that the usual animal research is not necessary for the licensing of a particular product.²¹⁸

The development of NAMs is important for companies too, since it could help them to reduce costs. The earlier in the process effects in the ultimate context of use are identified, the more efficiently

²¹³ For example, on an online platform such as preclinicaltrials: <https://preclinicaltrials.eu/>

²¹⁴ Proefdiervrij, 'Helpathon: help mee proefdiervrije wetenschap te versnellen' ['Helpathon: help to accelerate animal-free science'].

²¹⁵ Wu et al., 'DrugSim2DR'.

²¹⁶ See, for example, European Commission, 'Report of the European Commission Workshop on "The Roadmap Towards Phasing Out Animal Testing for Chemical Safety Assessments"'.
²¹⁷ Schmeisser et al., 'New Approach Methodologies in Human Regulatory Toxicology – Not If, but How and When!'

²¹⁸ Chien et al., 'Re-evaluating the need for chronic toxicity studies with therapeutic monoclonal antibodies, using a weight of evidence approach'.

redundant research can be avoided.²¹⁹ *In silico* models help the pharmaceutical industry to make the medicine development process more efficient by identifying at an early stage the substances that are most likely to be effective.²²⁰ However, as explained above, even those promising NAMs cannot yet completely replace *in vivo* research.

²¹⁹ See, for example Ewart et al., 'Performance Assessment and Economic Analysis of a Human Liver-Chip for Predictive Toxicology'. The article describes a liver-chip organoid, which researchers believe could save the pharmaceutical industry almost three billion euros a year.

²²⁰ Madden et al., 'A Review of *In Silico* Tools as Alternatives to Animal Testing'.

NAMs	Relevant for NHP replacement	Accelerators	Obstacles	Short term ²²¹	Medium term	Long term
Systematic literature review ²²²	Yes	Publication of articles with uninformative data and/or unconfirmed hypotheses, and adherence to ARRIVE guidelines ²²³	Research with inadequate results, such as results based on an inadequate number of observations and/or unconfirmed hypotheses, is not being published. ²²⁴	Yes		
Organoids from adult and induced pluripotent stem cells	Yes	Further development with general immune system and vascularisation	Complexity, particularly of the specific immune system	Question-dependent, albeit at organ-level	Question-dependent, but probably at general immune-system level	Yes, probably also on specific immune responses
Organ-on-a-chip	Yes	Combination of one or several organs with the general immune system ²²⁵	Complexity of the specific immune system, vascular system and multiple organs ²²⁶	Question-dependent, albeit at organ-level	Yes, but probably at a general immune-system level	Yes

²²¹ It is difficult to estimate how soon NAMs could replace NHP research in practice. First of all, the future is, of course, inherently uncertain. A further complicating factor is that, in most cases, it will be necessary to use a combination of NAMs to replace an NHP study. Thirdly, as the committee has explained in this chapter, the NAM landscape is characterised by a very wide spectrum of novel methods and techniques, implying that any schematic periodisation is inevitably simplistic. The committee's period estimates are based on its interviews with NAM researchers and on literature review. See, for example: Hartung, Maertens and Luechtefeld, 'E-Validation – Unleashing AI for Validation'. Escher et al., 'Development of a Roadmap for Action on New Approach Methodologies in Risk Assessment'. Low et al., 'Organs-on-Chips'.

²²² Systematic literature review is not actually an NAM, but is included in this table because the practice can play an important role in reducing NHP research.

²²³ The ARRIVE guidelines are "a checklist of information to include in publications describing animal research. They ensure that studies are reported in enough detail to add to the knowledge base. This transparency enables readers and reviewers to scrutinise the research adequately, evaluate its methodological rigour, and reproduce the methods or findings." NC3R, 'The ARRIVE Guidelines 2.0: Updated Guidelines for Reporting Animal Research. Originally Published in PLOS Biology, July 2020.'

²²⁴ Bernard et al., 'Fiddle'.

²²⁵ Janssen et al., 'Biofabrication Directions in Recapitulating the Immune System-on-a-Chip'.

²²⁶ Regarding the immune system, see, for example, Maharjan, Cecen and Zhang, '3D Immunocompetent Organ-on-a-Chip Models'.

Bio-printed tissues	Maybe	Concentration on cultivation of cells on scaffolds ²²⁷	Development in living cells without scaffolding ²²⁸	Basic tissue prints	Cell planting and starting bioprinted tissues	Yes
<i>Ex vivo</i> tissue cultures	Yes	Availability of organ material to the scientific community	Bureaucracy due to ethical considerations relating to supplying laboratories	Yes		
<i>In silico</i> models	Yes	Combination with other NAMs	Unilateral application	Very well developed	Yes	
Open and big data with AI	Yes	Combination with other NAMs	Unilateral application	Very well developed	Yes	
Biobanks	Yes			Available, further development in progress	Available, further development in progress	Yes
Use of human volunteers and patient research	Yes	Standardisation of manner of use and applicable rules	Bureaucracy due to ethical considerations	Yes		
Human data	Yes	Standardisation of manner of use and applicable rules	Bureaucracy due to ethical considerations	Yes		

Table 4 Overview of NAMs

²²⁷ Rider et al., 'Bioprinting of Tissue Engineering Scaffolds'.

²²⁸ Ghosh, 'Prospects of Emerging 3D Bioprinting Technologies'.

PART II Policy scenarios

Four policy scenarios for dealing with NHP experiments

In Part 1, the committee reported on its investigation. The committee's main task was to investigate the scope for further reducing the number of experiments on NHPs without affecting research that is strictly required for the control of life-threatening diseases and outbreaks of infectious diseases that threaten public health. To that end, the committee considered the general topic of NHP research in several distinct steps. That yielded clear and unambiguous answers to a number of sub-questions: regarding the historical and societal background to NHP experiments, regarding the ethical-philosophical frameworks that might be applied, regarding the relevant national and international laws and regulations, regarding NHP facilities in the Netherlands, regarding the numbers of NHP experiments carried out in the Netherlands, and regarding many aspects of international NHP research (see the introductory chapter for a more complete overview).

However, there is no consensus in the academic community regarding certain other important sub-questions. The main questions about which consensus is lacking relate to the translatability of NHP research, the importance of NHP research for various scientific fields, the prospects for the development of NAMs, and the most appropriate ethical framework to apply. Where such questions are concerned, the committee has sought to provide the most complete picture it can of the various, often conflicting views held by different parties.

It is not possible to give clear scientific advice regarding matters where academic consensus is absent. Where science does not provide a decisive basis for decision-making, political and policy choices will be required, taking the scientific background into account. Therefore, in this second part of the report, the committee presents four policy scenarios for possible future developments in the use of NHPs. In its definition of the various scenarios, the committee seeks to address all the main aspects of the future use of NHPs, including:

- The scientific value of NHP research
- The relative translatability of NHP research
- The development of NAMs
- The roles of international regulatory bodies such as the EMA and national bodies such as the CBG, CCMO and CCD
- The ethical aspects of animal research in general and NHP research in particular
- The symbolic significance of NHPs within the wider issue of animal research
- The legal aspects of using NHPs
- The economic aspects, including operational costs, capital costs and potential returns
- The role of industry
- Societal resistance to and unease about the use of NHPs in research
- The societal need to control infectious diseases that threaten public health (in other words: pandemic preparedness)
- The societal need to control life-threatening and other diseases
- The position of the Netherlands in Europe and the wider world

On the basis of those aspects, four policy scenarios have been developed, each outlining a different possible future for the use of NHPs. The policy scenarios have been defined by assuming various

policy decisions are made regarding the above-mentioned aspects – about which scientific consensus is lacking. From the assumed policy decisions, a wide variety of implications can be deduced. By taking that approach, the committee is responding to the minister’s stated wish: “I am emphatically not asking for policy advice, but for an examination of what can and cannot be done.”²²⁹ For a comparative overview of the four scenarios, see [Table 5](#).

The committee notes that the four presented scenarios are not the only possible policy scenarios. They have been chosen because collectively they provide a good reflection of all the policy decisions that might be made. The committee can easily envisage a policy being formulated that combines elements of the various scenarios. Furthermore, the landscape is dynamic, particularly as a consequence of successful NAM research. As a result, future policy choices in certain areas may differ from those that would be made today.

At the end of each policy scenario description, the committee briefly outlines the costs, benefits and risks that the scenario is expected to yield. Like many things pertinent to the debate regarding NHP research, the costs, benefits and risks expected to arise depend on the viewpoint from which assessment is made, and on the values applied. The committee has nevertheless sought to provide the most neutral summary it can. Aspects that have no obvious implications for costs, benefits and risks are not addressed in the committee’s summaries; nor are aspects that are common to all four policy scenarios. Further details are given in [Tabel 5](#) and in the scenario descriptions.

Finally, it is important to note that the policy scenarios have a great deal in common. Whatever choices are made, the following points will remain valid in the future in all four scenarios:

- In all scenarios, the current licensing practices (of the DEC’s and CCD) must ensure that NHP research is undertaken only in circumstances where a clear scientific benefit is expected, which is commensurate to the discomfort that the NHPs will experience, and where all research is conducted according to high standards of care. Such harm-benefit analyses are not easy to make, and the DEC’s and CCD frequently consider possible adaptations.
- NAM research will continue, not only with a view to finding alternatives to NHP experiments. Many NAM researchers expect significant development in the coming years, but also agree that NHP research will remain necessary for the time being. Moreover, NAMs vary greatly and are at very different stages of development. It is therefore important that NAM research continues to receive support.²³⁰ That may also have a positive effect on the Netherlands’ attractiveness to companies in this sector, thus reinforcing the Netherlands’ pioneering role in this field, where it already has a prominent international position.
- Regulatory bodies such as the EMA (in Europe), the FDA (in the US) and the CBG (in the Netherlands) are actively involved in seeking alternatives to animal testing in general and NHP experiments in particular. That is reflected in their willingness to accept arguments based on ‘weight of evidence’ rather than animal research findings, and in their active dialogue with industrial and university researchers regarding the development of NAMs that could replace animal research in the context of licensing procedures.
- In all scenarios, the aim is to continue conducting excellent scientific research, if possible with fewer NHP experiments. It is therefore advisable that roadmaps like the one used to guide progress towards animal-free research are refined or developed for the NHP-relevant

²²⁹ Minister of OCW, Voortgang onderzoek verdere verlaging proeven op niet-humane primaten (motie Wassenberg c.s.) [Progress of research into the further reduction of experiments on non-human primates (motion by Wassenberg et al.)].

²³⁰ In view of the recent financial investments, the committee envisages not so much financial support as support in the form of research policy coordination, the modernisation of relevant scientific education, and the adaptation of regulatory frameworks and review practices.

fields of science. The existing roadmaps for neurosciences and immunology can be refined and implemented and a roadmap for infectious disease research can be developed. In line with the NCad review of the roadmap approach in 2024, that should be done in close consultation with civil society groups.

- In all the scenarios, it will be important that the Netherlands pursues European coordination and collaboration in NHP research and NAM research.²³¹ That could involve, for example, collaborating on vaccine development and pandemic resilience, or on NAM development, or taking a coordinated approach to the use of NHPs and the phase-out of NHP use where possible. In the latter context, the Netherlands should advocate a roadmap approach, with NHP use linked to the challenges facing society and unanswered scientific questions, rather than reflecting the habitual practice of using NHPs for certain research purposes (see also the preceding point).
- Generally speaking, scientific researchers carry out thorough literature reviews before setting up a new study. Nevertheless, systematic literature reviews are particularly important in relation to animal research in general and NHP research in particular, as a means of establishing that a proposed study is necessary, insofar as the research question could not be answered on the basis of earlier research. In all the policy scenarios, systematic literature reviews should therefore play a central role.
- It is very important that the rationale for deciding to pursue a particular scenario, and for the decisions made in the context of that scenario, is set out as transparently as possible. The Dutch public appears to attach great importance to the proportionality principle in ethical judgements relating to animal research: people expect the potential benefit of animal research to be in proportion to the anticipated burden on the animals involved.²³²
- The Netherlands' international competitiveness and capacity for innovation depend on many different factors, and especially on the amount of scientific research done in the Netherlands and the nature of that research. NHP research accounts for a very small portion of all research undertaken in the Netherlands. The implications for the nation's innovation capacity of continuing or discontinuing NHP research cannot therefore be determined. Consequently, the policy scenarios do not differ in terms of the impact on innovation capacity either.
- The legal framework for NHP research is defined by the Wod (Experiments on Animals Act) and by European directives. All four policy scenarios fit within that legal framework.
- Under all policy scenarios, publication practice can be improved by requiring the preregistration of animal experiments and the application of ARRIVE guidelines.²³³

In scenarios 2, 3 and 4, where Dutch government support for the BPRC continues, NAM research at the BPRC should be expanded and linked more firmly to NAM research at the various (Dutch) universities. The linkage of data from (old) NHP research to NAM development is a promising strategy.²³⁴ In that context, it would also be helpful if the BPRC were allowed to apply directly to NWO and ZonMw for funding in the role of principal investigator. At the same time, the BPRC can be more transparent about how many NHPs of which species are used for particular tests. If the Netherlands

²³¹ See also the European Commission's proposal in response to a Citizens' Initiative: 'EU Commission response to Citizens' Initiative "Save Cruelty-Free Cosmetics – Commit to a Europe without Animal Testing"'.

²³² Rathenau Instituut, 'Ethische overwegingen rond dierproeven spelen meer dan ooit een rol' ['Ethical considerations relating to animal research play a greater role than ever']. Mendez et al., 'Openness about Animal Research Increases Public Support'.

²³³ NC3R, 'The ARRIVE Guidelines 2.0: Updated Guidelines for Reporting Animal Research. Originally Published in PLOS Biology, July 2020.' With regard to the value of the pre-registration of animal research, see Naald et al., 'Preregistration of animal research protocols'.

²³⁴ For an example of synergy between NHP research and NAM research, see: Tanner et al., 'A Non-Human Primate in Vitro Functional Assay for the Early Evaluation of TB Vaccine Candidates'.

were to opt for one of those three scenarios, such transparency may be expected to bolster support for NHP research.

Policy scenario 1: Phasing out NHP research ²³⁵	Policy scenario 2: Reduction of NHP research (<i>two sub-scenarios a and b</i>)	Policy scenario 3: Continuation of NHP research	Policy scenario 4: Possible increase in NHP research ²³⁶
<p>Translatability of NHP models to humans is not considered good enough to justify NHP research</p>	<p>Translatability of NHP models to humans is considered good enough to justify some NHP research</p>	<p>Translatability of NHP models to humans is considered good enough to justify some NHP research</p>	<p>Translatability of NHP models to humans is considered good enough to justify some NHP research</p>
<p>Colony of NHPs at the BPRC to be phased out by stopping breeding; the BPRC closes after last 'retired' primate dies²³⁷</p>	<p>BPRC colony remains at current size (for necessary genetic diversity); research capacity (people and laboratories) is maintained by continuation of research into infectious diseases that threaten public health (sub-scenario 2a) or research into some life-threatening and otherwise serious diseases (sub-scenario 2b); possible phase-out of brain research with NHPs at the NIN and displacement to the BPRC (depending on KNAW policy)</p>	<p>BPRC colony remains at current size (for necessary genetic diversity); possible phase-out of NHP research at the NIN (depending on KNAW policy)</p>	<p>Depending on decisions made at the European level, the BPRC colony is enlarged; possible continuation of NHP research at the NIN (depending on KNAW policy)</p>
<p>Dutch research loses the key role that the BPRC plays in international cooperation</p>	<p>Dutch research loses the key role that the BPRC plays in international cooperation, but retains the capacity to quickly join international efforts in the event of a pandemic</p>	<p>Dutch research retains current international position due to NHP research agenda remaining unchanged: infectious diseases that threaten public health, life-threatening and otherwise serious diseases, and (depending on KNAW policy) neurological disorders</p>	<p>If the Netherlands is selected as a European centre for NHP research, the Netherlands strengthens its international position due to more NHP research potentially being carried out, including research into conditions not currently under investigation</p>
<p>Where the preference is nevertheless to use an NHP model, Dutch research becomes more dependent on international cooperation</p>	<p>Where the preference is nevertheless to use an NHP model, Dutch research becomes more dependent on international cooperation</p>		

²³⁵ In this table, for the sake of brevity, NHP research is discussed as if all NHP experiments were similar. That is not the case: there are major differences in the contexts in which NHPs are used. Moreover, the possibility of using a combination of NAMs instead of NHPs must be considered in relation to each research question individually. Where that is not possible, the CCD must also consider each NHP experiment individually to assess conformance to the licensing criteria in its harm-benefit analysis. Furthermore, no regulatory research is carried out in the Netherlands using NHPs, although the use of NAMs is expected to replace NHP research in that area before replacement is possible in basic research and translational research, which are carried out in the Netherlands.

²³⁶ The development of Scenario 4 – which involves an increase in the number of NHP experiments carried out – may seem to be at odds with the House of Representatives' request for the possibility of reducing the number of NHP experiments to be investigated. The committee has nevertheless developed scenario 4 in accordance with its remit to also report on international developments, having established that, in some countries, the number of NHP experiments is increasing. The coordination of NHP research and the centralisation of primate centres in Europe could also lead to a reduction in the total number of NHP experiments carried out in Europe.

²³⁷ It is conceivable that an organisation other than the BPRC will take care of primates currently housed at the BPRC when they are 'retired'.

NAMs are considered good enough, even in the short term, to justify the phase-out of NHP research

Good NHP research and some good researchers may move abroad

The phasing out of NHP research implies a paradigm shift

NAMs are considered to have sufficient promise, even in the short term, to justify a reduction in NHP research

Good NHP research and some good researchers may move abroad

Substantial reduction in NHP research implies a paradigm shift

NAMs not expected to be good enough in the short term to justify a substantial reduction in the number of NHP experiments

NAMs not expected to be good enough in the short term to justify a substantial reduction in the number of NHP experiments

Ethical choices and implications

If the moral equality of NHPs and humans is adopted as an ethical principle, only policy scenario 1 is acceptable. Implication: the use of medicines from abroad developed by means of NHP research is unethical.

However, even if a utilitarian or other ethical framework is adopted, policy scenario 1 may be seen as the most desirable scenario if the quality of the relevant NAM models is considered greater than that of the available NHP models.

'Ethical burden' of doing NHP research is transferred to other countries if the Netherlands continues to enjoy the benefits of NHP research carried out elsewhere

Human interests (society's greater pandemic preparedness [in sub-scenario 2a] or the ability to control life-threatening and otherwise serious diseases [sub-scenario 2b]) are considered to prevail over NHPs' interests.

'Ethical burden' of doing certain NHP research is transferred to other countries if the Netherlands continues to enjoy the benefits of such NHP research carried out elsewhere

Human interests (society's greater pandemic preparedness and the ability to control life-threatening and otherwise serious diseases) are considered to prevail over NHPs' interests.

NHPs' interests are considered less important than opportunities to successfully prevent and treat human conditions that have high disease burdens, although, in this scenario, there is very likely to be a considerable reduction in the number of NHPs used for research at the European level

Legal choices and implications

Cessation of government funding of the BPRC

Certain research may be permitted or prevented by attaching conditions to government funding of the BPRC; in that context, a choice must be made between two policies:

1. Sub-scenario 2a or 2b?
2. If sub-scenario 2b: which life-threatening and otherwise serious diseases may and may not be investigated by means of NHP research?

Organisations (including universities and companies, or the BPRC if funded by other means) may continue to conduct research in the Netherlands using NHPs (if approved by the CCD), since it is permitted under the EU directive.

NHP research at the NIN to be phased out, depending on KNAW decision-making

Economic choices and implications

Government relieved of the cost of funding the BPRC; government must meet the cost of retiring the BPRC colony²³⁸

BPRC's structural cost base remains unchanged because the minimum colony size remains the same, due to the need to retain genetic diversity.

BPRC's structural cost base remains unchanged because the minimum colony size remains the same, due to the need to retain genetic diversity.

Possible enlargement of the BPRC colony implies additional cost, but borne in principle by the EU if enlargement is part of a new EU policy of NHP facility centralisation

Future vaccine development in the Netherlands is reliant on the use of NHPs abroad until NAMs are considered good enough to be accepted by the EMA/CCD for preclinical testing

(The cost of research will depend on the policy choices made in connection with the sub-scenarios, but the cost is met largely by external bodies, such as the NWO, ZonMw, EU, ERC and NIH²³⁹)

Potentially positive economic effects due to the Netherlands playing a more central role in European NHP research

Possible additional costs for companies and research institutions that start commissioning NHP research abroad

Societal choices and implications

In light of the expert interviews conducted by the committee and parliamentary debate on this topic, the committee believes that the complete phase-out of NHP research is probably in line with mainstream Dutch public opinion.²⁴⁰

In light of the expert interviews conducted by the committee and parliamentary debate on this topic, the committee believes that the reduction of NHP research is probably in line with mainstream Dutch public opinion.²⁴⁰

In light of the expert interviews conducted by the committee and parliamentary debate on this topic, the committee believes that the continuation of NHP research is probably not in line with mainstream Dutch public opinion.²⁴⁰

In light of the expert interviews conducted by the committee and parliamentary debate on this topic, the committee believes that the expansion of NHP research is probably not in line with mainstream Dutch public opinion.²⁴⁰ What the balance of opinion would be if the expansion of Dutch NHP research were part of a net reduction at the European level is as yet uncertain

²³⁸ It is conceivable that an organisation other than the BPRC will take care of primates currently housed at the BPRC when they are 'retired', but the cost must still be met.

²³⁹ Research will be funded largely by bodies such as the NWO, ZonMw, EU ERC and NIH in all the policy scenarios.

²⁴⁰ For an overview of public opinion on animal-related matters, see: Raad voor Dierenaangelegenheden (Council on Animal Affairs), 'Staat van het Dier 2024' [Status of the Animal 2024]. See also the following European Citizens' Initiative: 'European Citizens' Initiative "Save Cruelty-Free Cosmetics – Commit to a Europe without Animal Testing"'.

International choices and implications

Netherlands unable to respond rapidly to an infectious disease outbreak with its own NHP research, leading to higher costs and risks in a pandemic

Certain civil society groups (especially patients associations) may be disappointed

NHP research in the Netherlands is expected to contribute to the treatment of infectious diseases that threaten public health (sub-scenario 2a) or to the treatment of as yet unspecified life-threatening and otherwise serious diseases (sub-scenario 2b).

Certain civil society groups (especially patients associations) may be disappointed

NHP research in the Netherlands is expected to contribute to the treatment of infectious diseases that threaten public health and to the treatment of life-threatening and otherwise serious diseases.

Certain civil society groups (especially animal welfare organisations) are disappointed.

More pandemic and life-threatening and otherwise serious diseases could potentially be prevented or treated on the basis of research carried out in the Netherlands.

Certain civil society groups (especially animal welfare organisations) are disappointed, unless the European coordination of NHP centres and research leads to a substantial reduction in overall NHP use.

Possible reduction in the overall number of NHP experiments in Europe if there is extensive coordination of NHP facilities.

No Dutch contribution to high-quality European NHP facilities through the BPRC.

Greater dependence on foreign countries (also during pandemics).

The Netherlands takes a pioneering role and actively seeks international support for this policy (EMA, EU, OECD).

The Netherlands continues to play a prominent role in international debate regarding the development and use of NAMs.

The Netherlands makes a small contribution to high-quality European NHP facilities through the BPRC.

Greater dependency on other countries for research for which the policy decisions made in sub-scenarios 2a and 2b imply that NHP research is not permitted.

The Netherlands takes a pioneering role and actively seeks international support for this policy (EMA, EU, OECD).

The Netherlands continues to play a role in debate regarding the scientific use of NHPs and other animals, and regarding the development and use of NAMs.

The Netherlands contributes to a European network of high-quality NHP facilities through the BPRC.

The Netherlands remains actively involved in policy to make NAMs more acceptable as a replacement for NHP experiments under EU regulations (EMA, EU, OECD).

The Netherlands continues to play a role in debate regarding the scientific use of NHPs and other animals, and regarding the development and use of NAMs.

The Netherlands contributes to a European network of high-quality NHP facilities regardless of where those facilities are based.

Consistent with the trend of increasing NHP research activity seen in some other countries.

The Netherlands remains actively involved in policy to make NAMs more acceptable as a replacement for NHP experiments under EU regulations (EMA, EU, OECD).

The Netherlands continues to play a role in debate regarding the scientific use of NHPs and other animals, and regarding the development and use of NAMs.

Table 5 Overview of policy scenarios

1 Phasing out NHP research in the Netherlands

Scenario description

In policy scenario 1, the Dutch government decides to stop funding the BPRC. Existing research on NHPs is phased out and public funding of the BPRC as a research facility and of NHP research will cease.²⁴¹ Sufficient funding remains necessary to enable the BPRC to properly house its primates during their 'retirement' – until the last monkey dies.²⁴²

An important consideration in that context is that, according to some, NAM-based research and research performed directly on human subjects have the potential to satisfy high scientific quality requirements without the use of NHPs, because NHP models are less translatable to humans than is often assumed. Not everyone accepts that view. Many researchers, including NAM researchers, still see NHP models as a necessary component of research into infectious diseases and life-threatening and otherwise serious diseases. Such researchers believe that one implication of this policy scenario is that the quality of Dutch research into infectious diseases and life-threatening and otherwise serious diseases would be adversely affected.

Two distinct ethical frameworks can be used to argue in favour of this scenario. The first is a deontological framework, within which humans and NHPs are considered morally equal, implying that the use of NHPs for the benefit of humans is unacceptable. The second is a utilitarian ethical framework, within which this policy scenario can be justified if the benefits of NHP research do not outweigh the harm caused to the NHPs involved.

This policy scenario does not preclude organisations (companies, universities and even the BPRC if funded by non-governmental sources) from carrying out NHP research in the Netherlands, if it is approved by the CCD.

Scientific choices and implications

Ending NHP research in the Netherlands would have implications for science, but they are difficult to predict precisely. There is no scientific consensus as to what implications ending NHP research would have for knowledge development.

Crucially in the context of this policy scenario, some people believe that NHP research could be phased out without any significant adverse effect on the quality of science and, indeed, that there could even be a positive effect. According to that school of thought, the translatability of NHP research to humans is poor, and NHP research is carried out mainly because it is still requested by regulatory bodies. Other research methods (NAMs) are also suitable, and sometimes better, for assessing whether a treatment is effective in humans. The phase-out of NHP research could be accommodated by promoting NAMs and revising the regulatory framework that governs the licensing

²⁴¹ In principle, it is possible for the BPRC to secure alternative funding to compensate for the loss of structural funding from OCW. As long as the facility complies with legal requirements, such a primate centre could not be prohibited.

²⁴² It is conceivable that another organisation takes care of the NHPs in 'retirement', but funding would still be required.

of medicines. That would also enable the Netherlands to retain its pioneering international role in NAM research.

Other people believe that, at least in the short term, NAMs would not be able to compensate entirely for the cessation of NHP research, with the result that important research into certain diseases would no longer be possible. Leading researchers and important scientific research may then move to other countries. Some researchers also argue that preventing basic research with NHPs would hold back innovation and possibly research into the technologies and diseases of the future.

The BPRC would lose its role as an independent, publicly funded primate centre with high-quality NHP breeding and accommodation facilities. The Netherlands would not be involved in any future centralisation of NHP facilities in Europe.

On the other hand, the cessation of NHP research in the Netherlands could serve as a signal to the international scientific community, with the result that research with NHPs is viewed more critically and that research into and with NAMs is given a boost.

Dutch universities could become less attractive as potential partners in collaborative international NHP research projects, but more attractive for NAM research projects.

Ethical choices and implications

In the context of an ethical framework where NHPs and humans are considered morally equal, policy scenario 1 is the only acceptable choice. However, even if a utilitarian or other ethical framework is adopted, policy scenario 1 may be seen as the most desirable scenario if the quality of relevant NAM-based research is considered greater than that of NHP research.

If research on NHPs is phased out in line with an equality-centred ethical framework, it is pertinent to ask what stance the Netherlands would take on treatments developed partly by means of NHP research carried out elsewhere. Would the use of such treatments still be acceptable? The implication could be that technologies and therapies (such as vaccines, new brain implants and stem cell therapies) have to be tested using only NAMs, other animals or human subjects, accepting an associated risk to humans. If NHP-based medicines do continue to be used in the Netherlands, the entire 'ethical burden' of NHP research would be transferred to other countries, while the Netherlands continues to reap the benefits.

If NHP research is phased out in line with a utilitarian ethical framework (because NAMs yield such good results that NHP research is considered unacceptably inferior), the dilemma regarding the use of vaccines and medicines developed elsewhere using NHP research is less problematic: the cessation of NHP research would be a product of advances in NAM research, and there would be nothing unusual about continuing to draw upon findings made by old scientific and technical research.

If NHP research is phased out on the basis of such ethical considerations, the implications may reach far beyond the NHP research world. First, because it would prompt the question why the same ethical argument is not applicable to animals other than NHPs, which in turn has implications for the acceptability of animal research in general. Second, because it would mean that the way animals are treated in the context of scientific research is fundamentally different from the way they are treated in, for example, livestock farming and sport. However, setting those more far-reaching questions

aside, the phase-out of NHP research can be seen as consistent with a broader process of change in the way society views animals.

Legal choices and implications

NHP use is likely to be phased out if government funding is withdrawn from the BPRC. Such a move would be allowed by EU law, and would not require any form of legislative intervention.

However, NHP research could not be *prohibited* by Dutch law as long as EU law continued to allow it, subject to strict conditions. Consequently, if the government were to use funding policy as a means of phasing out NHP research, organisations such as private companies, universities and research institutions would still have the option of using NHPs, providing that the relevant legal requirements were met and the plans reviewed and approved by the CCD. In practice, however, any organisation taking that option would have to import NHPs, increasing the risk of zoonoses.

Economic choices and implications

Vaccine and medicine development in the Netherlands would become reliant on the use of NHPs abroad until NAMs are considered good enough to be accepted by the EMA/CCD for preclinical testing. That could mean that the Netherlands becomes less attractive to pharmaceutical companies. It should be noted, however, that industrial and university researchers would still be able to commission NHP research abroad, as they already do, although that would probably involve higher costs.

Funding of the BPRC would have to continue during the phase-out of the current colony, until all the animals died naturally.²⁴³

Societal choices and implications

In light of the expert interviews conducted by the committee and parliamentary debate on this topic, the committee believes that the complete phase-out of NHP research is probably in line with Dutch public opinion.²⁴⁴

Many Dutch people, and some patients associations in particular, attach great value to scientific research into certain conditions, even if it involves NHP experiments. Such people and organisations are therefore likely to be disappointed by a complete phase-out of NHP research in the Netherlands.

Phasing out NHP research in the Netherlands could lead to greater dependence on other countries in the event of a pandemic crisis, and to reduced access to and involvement in research into serious diseases.

International choices and implications

The Netherlands would actively seek international support for a policy of eliminating the need for NHP research. To that end, it would remain an active participant in EMA working groups and appropriate initiatives would be taken within the European Commission and the OECD.

²⁴³ Even if the NHPs were 'retired' to an external facility, funding would still be required.

²⁴⁴ For an overview of public opinion on animal-related matters, see: Raad voor Dierenaangelegenheden (Council on Animal Affairs), 'Staat van het Dier 2024' [Status of the Animal 2024]. See also the following European Citizens' Initiative: 'European Citizens' Initiative "Save Cruelty-Free Cosmetics – Commit to a Europe without Animal Testing"'.

Dutch politicians, policymakers and researchers would also (continue to) play a leading role in the broader international debate on phasing out the use of NHPs and other animals for scientific research.

The Netherlands would not contribute to a high-quality European NHP facility with the BPRC.

One implication of that policy is that researchers who do want to conduct NHP experiments would often do so abroad. In that context, the Netherlands would therefore become more dependent on cooperation with foreign researchers, also in the event of a pandemic.

The Netherlands would become isolated from international scientific developments in NHP research into infectious diseases, life-threatening diseases and brain disorders, insofar as research into such diseases continued to require the use of NHPs. In other countries, such as the US and China, the amount of NHP research being carried out is increasing considerably.

Cost, benefit and risk summary

The *benefit* of this policy scenario is that NHP research in the Netherlands would be phased out. (Qualification: any such phase-out would primarily involve NHP research at the BPRC; activities at other institutions, such as the NIN and pharmaceutical companies, are not under the Dutch government's direct control.) The *cost* of this policy scenario is the Netherlands' acceptance of complete dependency on other countries for research with NHPs. That would place the Netherlands in a difficult ethical position, insofar as it would not be doing its own NHP research but would be benefitting from medical innovations, such as new vaccines and medicines, developed partly by means of NHP research elsewhere. A further *cost* is increased dependency on foreign NHP research and a consequent reduction in the country's ability to respond to a future pandemic. The first *risk* associated with this policy scenario is that the Netherlands would no longer be able to monitor the quality of NHP facilities. The second *risk* is that good lines of research that involve the use of NHPs would be continued elsewhere, leading to the loss of knowledge and experience in the Netherlands.

2 Reduction of NHP research in the Netherlands

Scenario description

In policy scenario 2, the Netherlands decides to fund less NHP research at the BPRC, but not to phase out such research completely. The rationale for such a policy is that research into infectious diseases and some life-threatening and otherwise serious diseases still require the use of NHPs.

Underpinning the policy is the belief that NAMs are not yet good enough to replace all NHP research, and that NHP models are sufficiently translatable to humans and therefore an important element of research aimed at the control of infectious diseases that threaten public health and research into some life-threatening and otherwise serious diseases. It should be noted that not everyone shares that belief: critics argue that the translatability of some NHP research has not been adequately demonstrated.

Ethically, this policy scenario is based on the view that humans are morally superior to animals and that animals may be used for the benefit of humans if there are compelling human interests at stake.

This policy scenario could be realised through two distinct sub-scenarios involving the attachment of conditions to government funding of the BPRC. The sub-scenarios differ in terms of how the reduction in NHP research is achieved. In sub-scenario **2a**, only research into infectious diseases that threaten public health would be allowed. In sub-scenario **2b**, research into certain specified life-threatening and otherwise serious diseases would also be allowed. In other words, a policy decision would have to be made as to where the dividing line between permissible and non-permissible NHP research is drawn.

Scientific choices and implications

In this scenario, the translatability of NHP models to humans is considered good enough to justify some NHP research, especially in areas where alternative methods (NAMs) are not yet sufficiently reliable. That implies the BPRC continuing to play a key role in scientific research into infectious diseases, such as tuberculosis (sub-scenario 2a) and into other life-threatening and otherwise serious diseases (sub-scenario 2b). Research into other diseases would be phased out. Genetic diversity within the BPRC colony would be maintained by keeping the colony at its current size. However, fewer NHP experiments would be carried out.

The phase-out of NHP research at centres other than the BPRC (i.e. at the NIN, depending on KNAW policy) would mean that NHPs are no longer used in some fields of research (particularly brain research).

That implies a risk that some researchers, who rely on NHP models in their research, would move with their research to other countries where it was still allowed.

Although NAMs are becoming increasingly sophisticated, NHP models are still regarded as necessary in some scientific fields, such as research into pandemic infectious diseases. Broadly speaking, NAM researchers agree that the use of NHPs will remain necessary for some years to come.

Ethical choices and implications

Ethically, this scenario is based on the belief that human health and safety considerations outweigh the interests of NHPs. Nevertheless, stricter limits would be placed on the research, restricting it to those fields where the use of NHPs is deemed indispensable. In sub-scenario 2a, the welfare of NHPs is considered secondary to the human interest in protection against pandemic infectious diseases that threaten public health; in sub-scenario 2b, NHP welfare is additionally secondary to the human interest in protection against life-threatening and otherwise serious diseases, for which NHP research would be permitted in line with specific policy decisions.

The starting point for the definition of two sub-scenarios, between which a choice must be made, is the assumption that the importance of the research goal has a bearing on whether NHP research is justified, implying that the judgement can vary from case to case. The adoption of that starting point may give rise to debate as to why NHPs may be used in one case and not in another. In other words, as to where the dividing line between permissible and non-permissible NHP research should be drawn. Should a line be drawn between infectious diseases that threaten public health and all other diseases (sub-scenario 2a), or between some life-threatening or otherwise serious diseases and others (sub-scenario 2b)? In the context of decision-making on that question, public communication would be very important: transparency regarding the policy choices made and reasons why NHP research is considered necessary for research into certain diseases but not others would be vital for the retention of public support.

If research on NHPs were phased out in accordance with sub-scenario b, it would be pertinent to ask what stance the Netherlands should take on treatments developed partly by means of NHP research carried out elsewhere. Would the use of such treatments still be acceptable? The implication could be that technologies and therapies (such as vaccines, new brain implants and stem cell therapies) have to be tested using only NAMs, other animals or human subjects, accepting an associated risk to humans. If NHP-based medicines do continue to be used in the Netherlands, the entire 'ethical burden' of NHP research would be transferred to other countries, while the Netherlands continues to reap the benefits.

Legal choices and implications

The government can restrict certain forms of research by attaching conditions to its funding of the BPRC, in line with the chosen sub-scenarios. Funding policy can therefore be used to restrict or permit NHP research without coming into conflict with the Wod (Experiments on Animals Act) or European law. Research with NHPs carried out at other institutions, such as the NIN, could in principle be reduced further, but that would depend on the policy adopted by the KNAW.

In either of the two sub-scenarios, it would be very important to work with European partners to get the regulatory requirements changed. That should lead to better integration of NAMs into medical research, or to some research being carried out on human subjects directly. The licensing requirement that certain medicines and treatment procedures be tested on NHPs could then be removed.

Economic choices and implications

The BPRC's structural costs would remain unchanged because the NHP colony would have to be maintained at its current size in order to assure the necessary genetic diversity. Operational research costs are covered mainly by the EU, NIH, NWO and ZonMw. The financial implications of adopting either of the sub-scenarios would therefore apply mainly to those cash flows.

Societal choices and implications

In light of the expert interviews conducted by the committee and parliamentary debate on this topic, the committee believes that the reduction of NHP research is probably in line with mainstream Dutch public opinion.²⁴⁵ On the other hand, some civil society groups, such as patients associations representing people with diseases whose investigation is believed to depend on NHP research, may feel abandoned.

In the context of a choice between sub-scenario 2a and sub-scenario 2b and decision-making in scenario 2b, it would be important to clearly communicate the reasons for the choice made. The public attaches great importance to proportionality in ethical decision-making on animal research; people expect the human health benefits to be in proportion to the burden on the animals involved.²⁴⁶

International choices and implications

On the international stage, the Netherlands would, through the BPRC, make a modest contribution to the European network of high-quality NHP facilities for research into infectious diseases (sub-scenario 2a) and some life-threatening and otherwise serious diseases (sub-scenario 2b).

The Netherlands would become more dependent on other countries for research into life-threatening and otherwise serious diseases for which NHP research is considered necessary but for which NHP use is prohibited in line with decision-making in sub-scenario 2b. As a result, Dutch scientists working in the relevant fields would have to collaborate more with international partners.

Particularly within organisations such as the EMA, EU and OECD, the Netherlands would actively seek international support for a policy of reducing NHP research. The Netherlands would continue to play an active role in international debate regarding the use of NHPs and other animals for research, particularly by promoting NAMs.

Cost, benefit and risk summary

The first *benefit* of this policy scenario is that NHP research in the Netherlands would be reduced considerably (subject to the same qualification regarding the NIN and private companies made in connection with the first policy scenario). The second *benefit* is that the Netherlands would retain its own facility and the ability to contribute to vaccine development, and would thus maintain its pandemic preparedness. The BPRC would retain an NHP colony, and would continue to carry out research into infectious diseases that threaten public health, so that the facilities and skills needed for such pandemic vaccine development would be maintained. The *cost* of this scenario is the Netherlands' acceptance that some other lines of NHP research would be wound down, depending on which sub-scenario is adopted and what decisions are made in the context of that sub-scenario. That would place the Netherlands in a difficult ethical position, insofar as it would not be doing its own NHP research of certain types, but would be benefitting from medical innovations, such as new vaccines and medicines, developed partly by means of NHP research elsewhere. That would also create a *risk* of good researchers leaving the Netherlands for other countries, leading to the loss of knowledge and experience. A second *risk* associated with reducing NHP research is that certain types

²⁴⁵ For an overview of public opinion on animal-related matters, see: Raad voor Dierenaangelegenheden (Council on Animal Affairs), 'Staat van het Dier 2024' [Status of the Animal 2024]. See also the following European Citizens' Initiative: 'European Citizens' Initiative "Save Cruelty-Free Cosmetics – Commit to a Europe without Animal Testing"'.

²⁴⁶ Rathenau Instituut, 'Ethische overwegingen rond dierproeven spelen meer dan ooit een rol' ['Ethical considerations relating to animal research play a greater role than ever']. Rathenau Instituut.

of research might no longer be possible, due to NHP shortages or due to the required statistical power being unobtainable.

3 Maintaining NHP research in the Netherlands

Scenario description

In policy scenario 3, the Netherlands decides to continue doing the NHP research that is currently carried out. The main consideration behind that decision is the desire to prevent harm to society by continuing research into infectious diseases that threaten public health, into treatments for life-threatening and otherwise serious diseases and possibly into brain disorders (depending on KNAW policy).

In this policy scenario, there is continuing emphasis on the mandatory three Rs approach: replacing, reducing and refining NHP research. There is also a focus on further improving animal welfare and on performing systematic literature reviews in order to ensure that there is ample scientific justification for any use of NHPs.

NHP research is believed to remain essential for addressing certain scientific questions, especially in research into infectious diseases, immunology and the neurosciences. However, it is in principle possible that the criteria applied in harm-benefit analyses by the DEC and the CCD would be modified.

Scientific choices and implications

In this scenario, the scientific community in the Netherlands continues to justify NHP research on the basis of the translatability of the results to humans. NHP models are still considered necessary, both for answering complex medical questions, especially in the field of infectious diseases, neurodegenerative disorders and other life-threatening and otherwise serious diseases, and for basic research. The genetic diversity of the BPRC's NHP colony remains important, so the colony is maintained at its current size. Although the BPRC retains its role, brain research involving the use of NHPs may be phased out at other centres, depending on the policy adopted by the KNAW.

In the short term, NAMs are not expected to be sufficiently reliable to allow for a significant reduction in NHP research. Nevertheless, NAM research continues, as it does in all the other policy scenarios, in order to reduce the need for NHP research in the future.

Efforts are made to refine NHP research practices, potentially leading to better scientific results, since higher animal welfare standards can result in better data.

Ethical choices and implications

In this scenario, ethical decision-making starts from the basic assumption that human life has greater moral value than NHP life. That influences the way that competing interests are weighed up against one another: the human interest in tackling serious diseases – such as Parkinson's disease, cancer and conditions that lead to blindness – takes precedence over the welfare of NHPs. In particular, the human interest in pandemic preparedness remains a dominant factor in the ethical justification for continuing NHP research.

Legal choices and implications

Like the other three policy scenarios, this scenario is compatible with the current legal framework formed by the EU directives and the Experiments on Animals Act (Wod).

The regulations remain focused on assuring animal welfare and application of the three Rs. The further refinement of research practices can be encouraged without the need for legislative changes. For example, in the licensing process, the existing ethical review committees (the DEC's and CCD) could pay greater attention to application of the three Rs and to the way their application is accounted for.

Economic choices and implications

The BPRC continues to receive financial support as a publicly funded, high-quality primate centre. The BPRC's structural cost base remains unchanged because the need for genetic diversity means that the colony must be maintained at its current size.

The additional focus on refinement may lead to higher operational research costs – as a consequence of, for example, stricter ethical requirements that necessitate longer-duration research. However, the additional focus on refinement could also improve the scientific quality of research findings.

Societal choices and implications

In light of the expert interviews conducted by the committee and parliamentary debate on this topic, the committee believes that the continuation of NHP research is probably not well aligned with Dutch public opinion.²⁴⁷

On the other hand, this scenario may receive support from other civil society groups, such as patients associations that believe that NHP research contributes to the prevention and treatment of the diseases they are concerned with.

International choices and implications

On the international stage, the Netherlands would, through the BPRC, continue to contribute to the European network of high-quality NHP facilities. That would enable the Netherlands to collaborate with other countries that also use NHPs for scientific research and to participate in the coordination of international research on infectious diseases, life-threatening diseases and other serious conditions with high disease burdens.

At the same time, the Netherlands would remain involved in policies geared to making NAMs more acceptable as alternatives to NHP research in the context of the EU regulations. Through organisations such as the EMA, the European Commission and the OECD, the Netherlands would play a role in promoting animal-free research methods in the long term. The Netherlands would also continue to be involved in debates regarding the use of NHPs and other animals for research.

Cost, benefit and risk summary

The *benefit* of this policy scenario is that current research into infectious diseases that threaten public health and into life-threatening and otherwise serious diseases could continue. The *cost* of this scenario is the Netherlands' acceptance that there would be no reduction in NHP research.

²⁴⁷ For an overview of public opinion on animal-related matters, see: Raad voor Dierenaangelegenheden (Council on Animal Affairs), 'Staat van het Dier 2024' [Status of the Animal 2024]. See also the following European Citizens' Initiative: 'European Citizens' Initiative "Save Cruelty-Free Cosmetics – Commit to a Europe without Animal Testing"'.

Consequently, this policy scenario would entail the *risk* that insufficient account is taken of public discontent concerning the continuation of NHP research.

4 Possible expansion of NHP research in the Netherlands

Scenario description²⁴⁸

Policy scenario 4 allows for an increase in NHPs and NHP experiments in the Netherlands, if the research questions of the day cannot be adequately addressed using NAMs. A key consideration here is that the use of NHPs can play a major role in controlling infectious diseases that threaten public health, in treating life-threatening and otherwise serious diseases and in basic research. Criticism of the translatability of NHP experiments is acknowledged, but more systematic literature reviews are done to avoid experiments that, given the results of previous research, have little chance of success or are unnecessary. It should be noted that, in this policy scenario, it is also possible that the number of NHP experiments *does not* increase, because adequate NAMs become available, or because NHP research is centralised at the European level, but at a facility in another country.

Moreover, it would be essential in this scenario that, at the European level, the Netherlands advocates the centralisation of all NHP research at a single primate centre. The BPRC would be a candidate for designation as Europe's central facility, because it already plays a leading and highly respected role in NHP breeding, accommodation and research. That would lead to an increase in the number of NHPs housed in the Netherlands, but to a reduction in overall NHP use in Europe. Hence, the Netherlands would take on the ethical burden associated with keeping NHPs, on behalf of other European countries. In a scenario where all NHP accommodation and research is centralised at the European level, analogous to the strategies that have proved successful in space research and elementary particle physics, it is entirely possible that the chosen centre is not ultimately in the Netherlands, fundamentally altering the situation at the Dutch national level.

Scientific choices and implications

This policy scenario is based on the assumption that research on NHPs is adequately translatable to humans – an assumption that not everyone accepts. In this scenario, it is possible that more NHP research takes place in the Netherlands (including research into conditions that are not currently studied by means of NHP research), while there is a considerable net decline in the number of NHP experiments at the European level. That could result in the Netherlands becoming more attractive as a potential partner for international research initiatives in the relevant fields of research.

NHP research would therefore continue to play an important role, for example in research into new fields, such as xenotransplantation. Meanwhile, as the development of alternative methods progresses, such methods would increasingly displace NHP research. In the short term, however, NAMs would not be considered good enough to substantially reduce the number of NHP experiments. However, the Netherlands would continue to participate in NAM development.

²⁴⁸ The development of Scenario 4 – which involves an increase in the number of NHP experiments carried out – may seem to be at odds with the House of Representatives' request for the possibility of reducing the number of NHP experiments to be investigated. The committee has nevertheless developed scenario 4 in accordance with its remit to also report on international developments, having established that, in some countries, the number of NHP experiments is increasing. The coordination of NHP research and the centralisation of primate centres in Europe could also lead to a reduction in the total number of NHP experiments carried out in Europe.

This scenario implies the possible enlargement of the BPRC's NHP colony, so that enough primates are available to support the intensification of NHP research without compromising the quality of the colony. The Netherlands could also play a role in the centralisation of NHP research within Europe.

Ethical choices and implications

The ethical premise underpinning this scenario is that human life has greater moral value than NHP life. Hence, NHPs' interests are considered less important than opportunities to successfully prevent and treat conditions that have high disease burdens in the human population. This scenario could include an additional obligation to pursue the international coordination of expertise with NHPs. This policy scenario would involve the adoption of an ethical framework geared mainly to the refinement of research practices on the basis of the three Rs approach.

If NHP research in the Netherlands increases as a result of centralisation and coordination at the European level, the ethical burden borne by the Netherlands will increase, while that borne by other European countries decreases. By accepting a greater ethical burden, the Netherlands may increase its influence and ability to promote acceptance of the Dutch outlook on NHP research within the international research community.

Legal choices and implications

Like the other three policy scenarios, this scenario is compatible with the current legal framework formed by the EU directives and the Experiments on Animals Act (Wod).

The regulations would remain focused on assuring animal welfare and application of the three Rs (refine, reduce and replace). The further refinement of research practices can be encouraged without the need for legislative changes. For example, in the licensing process, the existing ethical review committees (the DEC's and CCD) could pay greater attention to application of the three Rs and to the way their application is accounted for.

Economic choices and implications

Economic activities that rely on scientific research (such as the biomedical industry) would benefit from the increased research activity, particularly if the Netherlands is able to play a role in the centralisation of NHP research within Europe. However, it is unclear whether that would also boost the capacity for innovation in the wider economy.

The size of the national NHP colony might need to be increased, thus driving up costs. Depending on what is decided regarding European centralisation, funding for expansion of the colony might be available from the EU. However, if European NHP research were centralised, but at a facility in another country, the Netherlands would be expected to contribute to the cost.

Societal choices and implications

In light of the expert interviews conducted by the committee and parliamentary debate on this topic, the committee believes that the expansion of NHP research is probably not well aligned with Dutch public opinion.²⁴⁹ On the other hand, this scenario may receive support from other civil society groups, such as patients associations.

²⁴⁹ For an overview of public opinion on animal-related matters, see: Raad voor Dierenaangelegenheden (Council on Animal Affairs), 'Staat van het Dier 2024' [Status of the Animal 2024]. See also the following European Citizens' Initiative: 'European Citizens' Initiative "Save Cruelty-Free Cosmetics – Commit to a Europe without Animal Testing"'.

However, European coordination of NHP research could lead to a considerable net reduction in the number of NHP experiments at the European level, if substantial centralisation is involved. The reason being that such an approach could reduce inefficient repetition or duplication of NHP research within Europe.

Increasing the number of NHP experiments in the Netherlands while also reducing the overall number performed within Europe could yield research findings that enable the prevention or treatment of additional serious diseases.

International choices and implications

The Netherlands would contribute to a European network of high-quality NHP facilities through the BPRC. The Netherlands would also be able to push for the coordination and centralisation of NHP facilities within Europe. However, any such centralisation would have to be conditional upon it leading to a net reduction in the number of NHP experiments carried out in Europe. Furthermore, the Netherlands would remain involved in the debate regarding the use of NHPs and other animals for scientific research, and in the development of policies designed to promote the acceptance of NAMs, including their acceptance as alternatives to NHP research.

This scenario is in line with the general international trend of collaboration and international coordination in research, and with the growth of NHP research in other countries. Some countries have recently enlarged their NHP colonies in order to carry out more NHP experiments, partly with a view to increasing their strategic independence.

Cost, benefit and risk summary

The *benefit* of this policy scenario is that additional NHP research would be possible, as well as the research already being carried out into infectious diseases that threaten public health and into life-threatening and otherwise serious diseases. While this policy scenario would allow for an increase in the number of NHP experiments, such an increase would not necessarily occur, because it is also possible that emerging NAMs would prove to be capable of answering the research questions that need to be addressed. The *cost* of this scenario is the Netherlands' acceptance that there would be no reduction in NHP research in the Netherlands itself, although there may be sound ethical reasons for doing so. Consequently, this policy scenario would entail the *risk* that insufficient account is taken of public discontent concerning the performance of NHP research.

In conclusion

In accordance with the establishment order that underpins the committee's work, the committee does not conclude this report with policy recommendations.²⁵⁰ The committee has sought to present the four policy scenarios in the most balanced and neutral way possible, in order to avoid any implicit suggestion of preference for one policy scenario or another. Each of the four policy scenarios can be defended on reasonable grounds – the ultimate adoption of one of them will depend on what political choices are made regarding matters about which it is not currently possible to give unequivocal and unanimous scientific advice.

It does not follow, however, that the committee does not wish to draw any conclusions. While the conclusions set out below do not constitute policy advice, they are relevant to the debate regarding the use of NHPs for scientific research, and to policy on the future of the BPRC.

First, we have been struck by the level of sincere commitment exhibited by all the experts we consulted – from active NHP researchers to outspoken animal rights activists, and the many who occupy the ground between those positions – during their cooperation with this investigation. That commitment was clear both during the public consultation phase and in the individual interviews conducted by the committee. The committee does not conclude that consensus in favour of one policy scenario or another can easily be found; but it does observe that all stakeholders were willing to listen to one another attentively, and to put forward reasoned arguments to support their own views. It should be noted that the people consulted by the committee are not responsible for the contents of this report and cannot be assumed to support some or all of its conclusions.

With regard to the substance of our investigation findings, the committee also considers it notable that the scientific staff of regulatory bodies such as the EMA, CBG and CCD are actively involved in seeking alternatives to NHP research in the context of the regulatory requirements. While it is true that efforts to change the regulatory requirements for new vaccines and medicines are proceeding slowly, that is a consequence of the need for diligence, not of any reluctance on the part of the regulatory bodies. In the search for alternatives to NHP research, a great deal can be achieved by working closely with the staff at the EMA, CBG and CCD, and especially by reaching out to those bodies at an early stage in the development process. Take, for example, the 'weight-of-evidence' approach, which is increasingly accepted by regulatory bodies: results obtained using a combination of research methods (e.g. previous animal research, research with human subjects and in vitro research) can be used by a manufacturer to argue that the usual animal research is not necessary for the licensing of a particular product.

The replacement of NHP research by NAMs will be possible in some research contexts sooner than in others. In most cases, replacement is likely to involve a combination of various NAMs. Our third general finding concerns the development of NAMs. There has been enormous progress in that field in recent years. For example, the Netherlands is held in high regard internationally because of its TPI Programme and excellent research into NAMs. However, it is notable that even NAM researchers believe that NHP research will remain necessary, at least for the next five years, especially in virology

²⁵⁰ Minister of OCW: "I am emphatically not asking for policy advice, but for an examination of what can and cannot be done." Minister of OCW, Voortgang onderzoek verdere verlaging proeven op niet-humane primaten (motie Wassenberg c.s.) [Progress of research into the further reduction of experiments on non-human primates (motion by Wassenberg et al.)].

and immunology and for vaccine development in the context of pandemic preparedness. Nevertheless, significant steps could be taken immediately to reduce the number of NHP experiments. If more systematic literature reviews were performed, NHP research into questions that are answerable without NHPs could be avoided. Moreover, NAMs should not be expected to replace NHP experiments on a one-to-one basis. It is the combination of various NAMs that is likely to yield the greatest benefit in practice. Furthermore, it will be important to follow a roadmap approach that is led not by the (replacement of) NHP experiments, but by the underlying research question, thus bringing into play very different research strategies that utilise NAMs and involve less NHP research, if any.

Fourthly, the committee wishes to confirm that the BPRC is a highly regarded primate centre, within both the national and international communities. The quality of its breeding activities and its accommodation facilities are particularly renowned. Interviewees from other countries commented on the importance of an institution that, being government-funded, can operate more independently of commercial interests than many other research centres. However, that does not imply that, if the Netherlands decides to retain the BPRC (policy scenarios 2, 3 or 4), improvements cannot be made. For example, the BPRC should do more systematic literature reviews before setting up new studies. A lot more could also be done to promote collaboration between the BPRC's recently created platform for alternatives and NAM researchers working at universities. Furthermore, the BPRC could be more transparent about the numbers and species of NHPs used in the various experiments. If policy scenario 2, 3 or 4 is adopted, such transparency could, the committee believes, help to secure support for NHP research in the Netherlands, especially if coupled with regular reporting on NAM research and the reduction of NHP use.

The committee's fifth observation relates to the international dimension of this issue. The NHP research policy choices made by the Netherlands will have implications for the country's international relations in a variety of fields. In that context, the Netherlands' (in)dependence in the event of a pandemic crisis is an important consideration. What effects do the different scenarios have on the Netherlands' pandemic preparedness? The committee has described the various effects in relation to each scenario. Another important consideration is international collaboration. There is still much to be gained from the coordination of NHP facility provision and NAM research, both separately and in combination, especially within Europe.²⁵¹

Finally, the committee wishes to stress that scientific development is so rapid that, in the short term, say the next five to ten years, the situation may change to an extent that makes other policy decisions possible.

²⁵¹ The *EU Roadmap Towards Phasing Out Animal Testing For Chemical Safety Assessments* is important in this context: European Commission, *Report of the European Commission Workshop on "The Roadmap Towards Phasing Out Animal Testing for Chemical Safety Assessments"*.

References

(including websites)

- Adams, S.R., E. Muchmore, en J.H. Richardson. *Non Human Primates in Biomedical Research*. Vol. Chapter 15-Biosafety, 1995.
<https://www.sciencedirect.com/science/article/abs/pii/B9780120886616500223>.
- Aid, Malika, Michaela Sciacca, Katherine McMahan, David Hope, Jinyan Liu, Catherine Jacob-Dolan, Olivia Powers, e.a. 'Mpox Infection Protects against Re-Challenge in Rhesus Macaques'. *Cell* 186, nr. 21 (12 oktober 2023): 4652-4661.e13. <https://doi.org/10.1016/j.cell.2023.08.023>.
- Albrecht, Laure, Elodie Bishop, Basile Jay, Blaise Lafoux, Marie Minoves, en Caroline Passaes. 'COVID-19 Research: Lessons from Non-Human Primate Models'. *Vaccines* 9, nr. 8 (10 augustus 2021): 886. <https://doi.org/10.3390/vaccines9080886>.
- Analistennetwerk Nationale Veiligheid. 'Themarapportage infectieziekten'. Den Haag, 2022.
- Anderson, D. J., en A. D. Kirk. 'Primate Models in Organ Transplantation'. *Cold Spring Harbor Perspectives in Medicine* 3, nr. 9 (1 september 2013): a015503-a015503.
<https://doi.org/10.1101/cshperspect.a015503>.
- Anderson, David en McCall, Kathy. 'Feasibility Study under Article 10 of Directive 2010/63/EU on Sourcing Non- Human Primates Only from Self-Sustaining Colonies'. Brussels: FRESCI, 10 november 2022.
- Andrykowski, Michael A., en William H. Redd. 'Life-Threatening Disease Biopsychosocial Dimensions of Cancer Care'. In *Medical Factors and Psychological Disorders*, onder redactie van Randall L. Morrison en Alan S. Bellack, 287-323. Boston, MA: Springer US, 1987.
https://doi.org/10.1007/978-1-4684-5230-3_12.
- Arluke, A., en C.R. Sanders. *Regarding animals*. Philadelphia: Temple University Press, 1996.
- Bailey, Jarrod. 'Arguments Against Using Nonhuman Primates in Research'. In *Nonhuman Primate Welfare: From History, Science, and Ethics to Practice*, onder redactie van Lauren M. Robinson en Alexander Weiss, 559-88. Cham: Springer International Publishing, 2023.
https://doi.org/10.1007/978-3-030-82708-3_23.
- . 'Monkey-Based Research on Human Disease: The Implications of Genetic Differences'. *Alternatives to Laboratory Animals* 42, nr. 5 (november 2014): 287-317.
<https://doi.org/10.1177/026119291404200504>.
- Bailey, Jarrod, en Michael Balls. 'Clinical impact of high-profile animal-based research reported in the UK national press'. *BMJ Open Science* 44, nr. 11 (20 oktober 2020).
<https://doi.org/10.1136/bmjos-2019-100039>.
- Bailey, Jarrod, en Katy Taylor. 'Non-Human Primates in Neuroscience Research: The Case against Its Scientific Necessity'. *Alternatives to Laboratory Animals* 44, nr. 1 (1 maart 2016): 43-69.
<https://doi.org/10.1177/026119291604400101>.
- Barclay, Amy M., Dennis K. Ninaber, Suzanne Van Veen, Pieter S. Hiemstra, Tom H. M. Ottenhoff, Anne M. Van Der Does, en Simone A. Joosten. 'Airway epithelial cells mount an early response to mycobacterial infection'. *Frontiers in Cellular and Infection Microbiology* 13 (26 september 2023): 1253037. <https://doi.org/10.3389/fcimb.2023.1253037>.
- Bateson, Patrick. 'Review of Research Using Non-Human Primates'. London: BBSRC, MRC, NC3RS, WellcomeTrust, 2011. https://wellcome.org/sites/default/files/wtvm052279_1.pdf.
- Bayne, Kathryn, Jann Hau, en Timothy Morris. 'The Welfare Impact of Regulations, Policies, Guidelines, and Directives and Nonhuman Primate Welfare'. In *Nonhuman Primate Welfare: From History, Science, and Ethics to Practice*, onder redactie van Lauren M. Robinson en Alexander Weiss, 643-60. Cham: Springer International Publishing, 2023.
https://doi.org/10.1007/978-3-030-82708-3_27.
- Belloir, Tiphaine, Sergio Montalvo-Vargo, Zabir Ahmed, Devon J. Griggs, Shawn Fisher, Timothy Brown, Maysamreza Chamanzar, en Azadeh Yazdan-Shahmorad. 'Large-Scale Multimodal

- Surface Neural Interfaces for Primates'. *iScience* 26, nr. 1 (januari 2023): 105866. <https://doi.org/10.1016/j.isci.2022.105866>.
- Bentham, J. *An Introduction to the Principles of Morals and Legislation*. Mineola, NY: Dover Philosophical Classics, 1789.
- Bernard, René, Tracey L. Weissgerber, Evgeny Bobrov, Stacey J. Winham, Ulrich Dirnagl, en Nico Riedel. 'Fiddle : A Tool to Combat Publication Bias by Getting Research out of the File Drawer and into the Scientific Community'. *Clinical Science* 134, nr. 20 (30 oktober 2020): 2729-39. <https://doi.org/10.1042/CS20201125>.
- Bibra, C. von, en R. Hinkel. 'Non-Human Primate Studies for Cardiomyocyte Transplantation—Ready for Translation?' *Frontiers in Pharmacology* 15 (17 juni 2024). <https://doi.org/10.3389/fphar.2024.1408679>.
- Bierlaagh, Marlou C., Anabela S. Ramalho, Iris A. L. Silva, Annelotte M. Vonk, Rutger M. van den Bor, Peter van Mourik, Johanna Pott, e.a. 'Repeatability and Reproducibility of the Forskolin-Induced Swelling (FIS) Assay on Intestinal Organoids from People with Cystic Fibrosis'. *Journal of Cystic Fibrosis* 23, nr. 4 (1 juli 2024): 693-702. <https://doi.org/10.1016/j.jcf.2024.04.014>.
- Bijker, Else M, Robert W Sauerwein, en Wiebe E Bijker. 'Controlled Human Malaria Infection Trials: How Tandems of Trust and Control Construct Scientific Knowledge'. *Social Studies of Science* 46, nr. 1 (februari 2016): 56-86. <https://doi.org/10.1177/0306312715619784>.
- Bijker, Wiebe E., Roland Bal, en Ruud Hendriks. *The Paradox of Scientific Authority: The Role of Scientific Advice in Democracies*. London, England; Cambridge, MA: MIT Press, 2009.
- Blaauboer, Bas J. 'Biokinetic Modeling and in Vitro-in Vivo Extrapolations'. *Journal of Toxicology and Environmental Health, Part B* 13, nr. 2-4 (17 juni 2010): 242-52. <https://doi.org/10.1080/10937404.2010.483940>.
- Bliss-Moreau, Eliza, Rama R. Amara, Elizabeth A. Buffalo, Ricki J. Colman, Monica E. Embers, John H. Morrison, Ellen E. Quillen, Jonah B. Sacha, Charles T. Roberts, en National Primate Research Center Consortium Rigor and Reproducibility Working Group. 'Improving Rigor and Reproducibility in Nonhuman Primate Research'. *American Journal of Primatology* 83, nr. 12 (december 2021): e23331. <https://doi.org/10.1002/ajp.23331>.
- Bonini, Luca, Cristina Rotunno, Edoardo Arcuri, en Vittorio Gallese. 'Mirror Neurons 30 Years Later: Implications and Applications'. *Trends in Cognitive Sciences* 26, nr. 9 (1 september 2022): 767-81. <https://doi.org/10.1016/j.tics.2022.06.003>.
- Bordes, E.C. 'Dieren in het geding Een juridisch-historische analyse van het verbod op dierenmishandeling'. PhD thesis. Utrecht: Universiteit Utrecht, 2010. <https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKewiRrePim7eFAxU7-QIHhXNmAncQFnoECBAQAQ&url=https%3A%2F%2Fdspace.library.uu.nl%2Fbitstream%2Fhandle%2F1874%2F188407%2FBordes.pdf%3Fsequence%3D1&usg=AOvVaw0CKxysBXbRZUL516ivXXhd&opi=89978449>.
- Bovenkerk, Bernice, en Frederike Kaldewaij. 'The Use of Animal Models in Behavioural Neuroscience Research'. In *Ethical Issues in Behavioral Neuroscience*, onder redactie van Grace Lee, Judy Illles, en Frauke Ohl, 17-46. Berlin, Heidelberg: Springer Berlin Heidelberg, 2014. https://doi.org/10.1007/7854_2014_329.
- BPRC. 'Ambitieplan BPRC - voor de periode 2019-2025', 2019. [https://www.bprc.nl/sites/default/files/downloads/1-2-2019_BPRC_Ambitieplan_2019-2025\[1\].pdf](https://www.bprc.nl/sites/default/files/downloads/1-2-2019_BPRC_Ambitieplan_2019-2025[1].pdf).
- . 'Biomedical Primate Research Centre', 2024. <https://www.bprc.nl/nl/home>.
- . 'BPRC's onderzoeksresultaten - De bijdrage van ons onderzoek aan de vooruitgang in de medische wetenschap', 2024. https://www.bprc.nl/sites/default/files/downloads/BPRC_Onderzoeksresultaten_2023.pdf.
- Bramer, Wichor M., Melissa L. Rethlefsen, Jos Kleijnen, en Oscar H. Franco. 'Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study'. *Systematic Reviews* 6, nr. 1 (6 december 2017): 245. <https://doi.org/10.1186/s13643-017-0644-y>.
- Brennan, Frank R., Joy Cavagnaro, Kathleen McKeever, Patricia C. Ryan, Melissa M. Schutten, John

- Vahle, Gerhard F. Weinbauer, Estelle Marrer-Berger, en Lauren E. Black. 'Safety testing of monoclonal antibodies in non-human primates: Case studies highlighting their impact on human risk assessment'. *mAbs* 10, nr. 1 (26 oktober 2017): 1-17. <https://doi.org/10.1080/19420862.2017.1389364>.
- Brown, Paul C., en Ronald L. Wange. 'Considerations Regarding the Use of Nonhuman Primates in Assessing Safety Endpoints for Pharmaceuticals'. *Regulatory Toxicology and Pharmacology* 143 (september 2023): 105449. <https://doi.org/10.1016/j.yrtph.2023.105449>.
- Brunner, Jessie W., Hanna C. A. Lammertse, Annemiek A. Van Berkel, Frank Koopmans, Ka Wan Li, August B. Smit, Ruud F. Toonen, Matthijs Verhage, en Sophie Van Der Sluis. 'Power and Optimal Study Design in iPSC-Based Brain Disease Modelling'. *Molecular Psychiatry* 28, nr. 4 (april 2023): 1545-56. <https://doi.org/10.1038/s41380-022-01866-3>.
- Buchanan-Smith, HM, AE Rennie, A Vitale, S Pollo, MJ Prescott, en DB Morton. 'Harmonising the Definition of Refinement'. *Animal Welfare* 14, nr. 4 (november 2005): 379-84. <https://doi.org/10.1017/S0962728600029717>.
- Burm, Saskia M., Jan-Bas Prins, Jan Langermans, en Jeffrey J. Bajramovic. 'Alternative Methods for the Use of Non-Human Primates in Biomedical Research'. *ALTEX - Alternatives to Animal Experimentation* 31, nr. 4 (1 november 2014): 520-29. <https://doi.org/10.14573/altex.1406231>.
- Capogrosso, Marco, Tomislav Milekovic, David Borton, Fabien Wagner, Eduardo Martin Moraud, Jean-Baptiste Mignardot, Nicolas Buse, e.a. 'A Brain-Spine Interface Alleviating Gait Deficits after Spinal Cord Injury in Primates'. *Nature* 539, nr. 7628 (november 2016): 284-88. <https://doi.org/10.1038/nature20118>.
- Carvalho, Constança, Augusta Gaspar, Andrew Knight, en Luís Vicente. 'Ethical and Scientific Pitfalls Concerning Laboratory Research with Non-Human Primates, and Possible Solutions'. *Animals* 9, nr. 1 (29 december 2018): 12. <https://doi.org/10.3390/ani9010012>.
- Casadevall, Arturo. 'The mRNA Vaccine Revolution Is the Dividend from Decades of Basic Science Research'. *The Journal of Clinical Investigation* 131, nr. 19 (1 oktober 2021). <https://doi.org/10.1172/JCI153721>.
- Cauvin, Annick J., Christopher Peters, en Frank Brennan. 'Advantages and Limitations of Commonly Used Nonhuman Primate Species in Research and Development of Biopharmaceuticals'. In *The Nonhuman Primate in Nonclinical Drug Development and Safety Assessment*, 379-95. Elsevier, 2015. <https://doi.org/10.1016/B978-0-12-417144-2.00019-6>.
- CCD. 'Aanvraagformulier projectvergunning', 21 maart 2023. <https://www.centralecommissiedierproeven.nl/documenten/formulieren/15/5/18/aanvraagformulier-projectvergunning>.
- . 'Centrale Commissie Dierproeven', 2024. <https://www.centralecommissiedierproeven.nl/>.
- . 'Herziene handreiking "Het genereren, fokken, genotyperen, monitoren en houden van genetisch gewijzigde dieren"'. Den Haag, 23 april 2024.
- . 'Onderzoekssamenvatting (NTS)', z.d. <https://www.centralecommissiedierproeven.nl/onderwerpen/niet-technische-samenvatting>.
- . 'Toelichting invullen formulieren aanvraag projectvergunning dierproef'. Centrale Commissie Dierproeven, 2016. <https://www.centralecommissiedierproeven.nl/documenten/formulieren/15/5/18/handleiding-aanvraag-projectvergunning-dierproeven>.
- . 'Wetten en regels', z.d. <https://www.centralecommissiedierproeven.nl/onderwerpen/wetten-en-regels>.
- Central Institute for Experimental Medicine and Life Science. 'Introduction', z.d. <https://www.ciea.or.jp/en/>.
- Chatfield, Kate, en David Morton. 'The Use of Non-human Primates in Research'. In *Ethics Dumping*, onder redactie van Doris Schroeder, Julie Cook, François Hirsch, Solveig Fenet, en Vasantha Muthuswamy, 81-90. SpringerBriefs in Research and Innovation Governance. Cham: Springer International Publishing, 2018. https://doi.org/10.1007/978-3-319-64731-9_10.
- Chaudhary, Namit, Drew Weissman, en Kathryn A. Whitehead. 'mRNA Vaccines for Infectious Diseases: Principles, Delivery and Clinical Translation'. *Nature Reviews Drug Discovery* 20, nr. 11 (november 2021): 817-38. <https://doi.org/10.1038/s41573-021-00283-5>.

- Chen, K. G., P. Zhong, W. Zheng, en J. M. Beekman. 'Pharmacological analysis of CFTR variants of cystic fibrosis using stem cell-derived organoids', 2019. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6856431/>.
- Chen, Xing, Feng Wang, Eduardo Fernandez, en Pieter R. Roelfsema. 'Shape Perception via a High-Channel-Count Neuroprosthesis in Monkey Visual Cortex'. *Science (New York, N.Y.)* 370, nr. 6521 (4 december 2020): 1191-96. <https://doi.org/10.1126/science.abd7435>.
- Chien, Hsiao-Tzu, Helen Prior, Laura Andrews, Leon van Aerts, Annick Cauvin, David O. Clarke, Kaushik Datta, e.a. 'Re-evaluating the need for chronic toxicity studies with therapeutic monoclonal antibodies, using a weight of evidence approach'. *Regulatory Toxicology and Pharmacology* 138 (1 februari 2023): 105329. <https://doi.org/10.1016/j.yrtph.2022.105329>.
- CIRCABC. 'Summary report on the statistics on the use of animals for scientific purposes in the EU and Norway (2020)', 2023. <https://circabc.europa.eu/ui/group/8ee3c69a-bccb-4f22-89ca-277e35de7c63/library/c957d77a-7a20-4a7c-9239-c73a833fd873/details?download=true>.
- Coleman, Kristine, Gregory Timmel, Kamm Prongay, en Kate C. Baker. 'Common Husbandry, Housing, and Animal Care Practices'. In *Nonhuman Primate Welfare: From History, Science, and Ethics to Practice*, onder redactie van Lauren M. Robinson en Alexander Weiss, 323-54. Cham: Springer International Publishing, 2023. https://doi.org/10.1007/978-3-030-82708-3_14.
- Collins, Francis S., en Lawrence A. Tabak. 'NIH plans to enhance reproducibility'. *Nature* 505, nr. 7485 (30 januari 2014): 612-13.
- Combes, Alain, Charles-Edouard Luyt, Jean-Yves Fagon, Michel Wolff, Jean-Louis Trouillet, Jean Chastre, en for the PNEUMA Trial Group. 'Early Predictors for Infection Recurrence and Death in Patients with Ventilator-Associated Pneumonia'. *Critical Care Medicine* 35, nr. 1 (januari 2007): 146. <https://doi.org/10.1097/01.CCM.0000249826.81273.E4>.
- Conroy, Gemma. 'How Wild Monkeys "Laundered" for Science Could Undermine Research'. *Nature* 623, nr. 7988 (16 november 2023): 672-73. <https://doi.org/10.1038/d41586-023-03533-1>.
- Corbett, Kizzmekia S. et al. 'Immune Correlates of Protection by mRNA-1273 Vaccine against SARS-CoV-2 in Nonhuman Primates'. *Science* 373 (17 september 2021). <https://doi.org/10.1126/science.abj0299>.
- Corbett, Kizzmekia S., Anne P. Werner, Sarah O'Connell, Matthew Gagne, Lilin Lai, Juan I. Moliva, Barbara Flynn, e.a. 'mRNA-1273 Protects against SARS-CoV-2 Beta Infection in Nonhuman Primates'. *Nature Immunology* 22, nr. 10 (oktober 2021): 1306-15. <https://doi.org/10.1038/s41590-021-01021-0>.
- Corradi, Marie, Thomas Luechtefeld, Alyanne M. De Haan, Raymond Pieters, Jonathan H. Freedman, Tamara Vanhaecke, Mathieu Vinken, en Marc Teunis. 'The Application of Natural Language Processing for the Extraction of Mechanistic Information in Toxicology'. *Frontiers in Toxicology* 6 (10 mei 2024): 1393662. <https://doi.org/10.3389/ftox.2024.1393662>.
- Dai, Lianpan, en George F. Gao. 'Viral Targets for Vaccines against COVID-19'. *Nature Reviews Immunology* 21, nr. 2 (februari 2021): 73-82. <https://doi.org/10.1038/s41577-020-00480-0>.
- Dam, Debby van, en Peter Paul De Deyn. 'Non-Human Primate Models for Alzheimer's Disease-Related Research and Drug Discovery'. *Expert Opinion on Drug Discovery* 12, nr. 2 (februari 2017): 187-200. <https://doi.org/10.1080/17460441.2017.1271320>.
- Daniel, Carola. 'Extracorporeal perfusion of isolated organs of large animals – Bridging the gap between in vitro and in vivo studies'. *ALTEX*, 2018, 77-98. <https://doi.org/10.14573/altex.1611291>.
- De Jongh, Dide, Emma K. Massey, the VANGUARD consortium, Ekaterine Berishvili, Laura Mar Fonseca, Fanny Lebreton, Kevin Bellofatto, e.a. 'Organoids: A Systematic Review of Ethical Issues'. *Stem Cell Research & Therapy* 13, nr. 1 (december 2022): 337. <https://doi.org/10.1186/s13287-022-02950-9>.
- De Lima-Pardini, Andrea C, Youstina Mikhail, Adan-Ulises Dominguez-Vargas, Numa Dancause, en Stephen H Scott. 'Transcranial Magnetic Stimulation in Non-Human Primates: A Systematic Review'. *Neuroscience & Biobehavioral Reviews* 152 (september 2023): 105273. <https://doi.org/10.1016/j.neubiorev.2023.105273>.
- De Swart, Rik L. 'Measles: What We Have Learned from Non-Human Primate Models'. *Drug Discovery Today: Disease Models* 23 (2017): 31-34. <https://doi.org/10.1016/j.ddmod.2018.01.002>.

- Deconinck, Frederik J. A., Ana R. P. Smorenburg, Alex Benham, Annick Ledebt, Max G. Feltham, en Geert J. P. Savelsbergh. 'Reflections on Mirror Therapy: A Systematic Review of the Effect of Mirror Visual Feedback on the Brain'. *Neurorehabilitation and Neural Repair* 29, nr. 4 (1 mei 2015): 349-61. <https://doi.org/10.1177/1545968314546134>.
- Denayer, Tinneke, Thomas Stöhr, en Maarten Van Roy. 'Animal models in translational medicine: Validation and prediction'. *European Journal of Molecular & Clinical Medicine* 2, nr. 1 (27 augustus 2014): 5. <https://doi.org/10.1016/j.nhtm.2014.08.001>.
- Dijkman, Karin, Nacho Aguilo, Charelle Boot, Sam O. Hofman, Claudia C. Sombroek, Richard A.W. Vervenne, Clemens H.M. Kocken, e.a. 'Pulmonary MTBVAC Vaccination Induces Immune Signatures Previously Correlated with Prevention of Tuberculosis Infection'. *Cell Reports Medicine* 2, nr. 1 (januari 2021): 100187. <https://doi.org/10.1016/j.xcrm.2020.100187>.
- Dijkman, Karin, Claudia C. Sombroek, Richard A. W. Vervenne, Sam O. Hofman, Charelle Boot, Edmond J. Remarque, Clemens H. M. Kocken, e.a. 'Prevention of Tuberculosis Infection and Disease by Local BCG in Repeatedly Exposed Rhesus Macaques'. *Nature Medicine* 25, nr. 2 (februari 2019): 255-62. <https://doi.org/10.1038/s41591-018-0319-9>.
- Du, Yuanyuan, Zhen Liang, Shusen Wang, Dong Sun, Xiaofeng Wang, Soon Yi Liew, Shuaiyao Lu, e.a. 'Human Pluripotent Stem-Cell-Derived Islets Ameliorate Diabetes in Non-Human Primates'. *Nature Medicine* 28, nr. 2 (februari 2022): 272-82. <https://doi.org/10.1038/s41591-021-01645-7>.
- Eastwood, D, L Findlay, S Poole, C Bird, M Wadhwa, M Moore, C Burns, R Thorpe, en R Stebbings. 'Monoclonal antibody TGN1412 trial failure explained by species differences in CD28 expression on CD4+ effector memory T-cells'. *British Journal of Pharmacology* 161, nr. 3 (oktober 2010): 512-26. <https://doi.org/10.1111/j.1476-5381.2010.00922.x>.
- Eaton, S. L., en T. M. Wishart. 'Bridging the Gap: Large Animal Models in Neurodegenerative Research'. *Mammalian Genome* 28, nr. 7-8 (augustus 2017): 324-37. <https://doi.org/10.1007/s00335-017-9687-6>.
- efpia. 'Putting Animal Welfare Principles and 3Rs into Action - European Pharmaceutical Industry Report - 2022 Update'. efpia.eu/media/637068/putting-animal-welfare-principles-and-3rs-into-action.pdf. Brussels, 2022. efpia.eu/media/637068/putting-animal-welfare-principles-and-3rs-into-action.pdf.
- Eichmüller, Oliver L., en Juergen A. Knoblich. 'Human Cerebral Organoids — a New Tool for Clinical Neurology Research'. *Nature Reviews Neurology* 18, nr. 11 (november 2022): 661-80. <https://doi.org/10.1038/s41582-022-00723-9>.
- EMA. 'EMA Guidance Document on the Use of Medicinal Products for Treatment and Prophylaxis in Case of Exposure to Biological Agents Used as Weapons of Terrorism, Crime or Warfare'. Amsterdam, 12 juli 2024.
- . 'Essential considerations for successful qualification of novel methodologies', 2017. https://www.ema.europa.eu/system/files/documents/other/wc500239928_en.pdf.
- . 'Ethical Use of Animals in Medicine Testing', 2025. <https://www.ema.europa.eu/en/human-regulatory-overview/research-development/ethical-use-animals-medicine-testing>.
- . 'Guideline on Similar Biological Medicinal Products Containing Monoclonal Antibodies – Non-Clinical and Clinical Issues'. London, 2012.
- Esbroeck, Annelot C. M. van, Antonius P. A. Janssen, Armand B. Cognetta, Daisuke Ogasawara, Guy Shpak, Mark van der Kroeg, Vasudev Kantae, e.a. 'Activity-Based Protein Profiling Reveals off-Target Proteins of the FAAH Inhibitor BIA 10-2474'. *Science (New York, N.Y.)* 356, nr. 6342 (9 juni 2017): 1084-87. <https://doi.org/10.1126/science.aaf7497>.
- Escher, Sylvia E., Falko Partosch, Sebastian Konzok, Paul Jennings, Mirjam Luijten, Anne Kienhuis, Victoria de Leeuw, Rosmarie Reuss, Katrina-Magdalena Lindemann, en Susanne Hougaard Bennekou. 'Development of a Roadmap for Action on New Approach Methodologies in Risk Assessment'. *EFSA Supporting Publications* 19, nr. 6 (2022): 7341E. <https://doi.org/10.2903/sp.efsa.2022.EN-7341>.
- Estes, Jacob D., Scott W. Wong, en Jason M. Brenchley. 'Nonhuman Primate Models of Human Viral Infections'. *Nature Reviews Immunology* 18, nr. 6 (juni 2018): 390-404. <https://doi.org/10.1038/s41577-018-0005-7>.

- European Chemicals Agency. *New Approach Methodologies in Regulatory Science: Proceedings of a Scientific Workshop. Helsinki, 19-20 April 2016*. Brussels: EU Publications Office, 2016. <https://data.europa.eu/doi/10.2823/543644>.
- European Parliament and Council. 'Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the Protection of Animals Used for Scientific Purposes'. Brussels, 2010.
- Europees Burger Initiatief. 'Voor cosmetica zonder dierenleed—maak Europa dierproefvrij', 2021. https://citizens-initiative.europa.eu/initiatives/details/2021/000006_nl.
- Europese Commissie. 'ALURES'. Geraadpleegd 5 december 2024. <https://webgate.ec.europa.eu/envdataportal/web/resources/alures/submission/nts/list>.
- . 'Mededeling van de commissie over het Europees burgerinitiatief (EBI) "Voor cosmetica zonder dierenleed — maak Europa dierproefvrij"'. Brussel, 2023. [https://ec.europa.eu/transparency/documents-register/detail?ref=C\(2023\)5041&lang=nl](https://ec.europa.eu/transparency/documents-register/detail?ref=C(2023)5041&lang=nl).
- . *Report of the European Commission Workshop on "The Roadmap Towards Phasing Out Animal Testing for Chemical Safety Assessments": Brussels, 11-12 December 2023*. Brussels: EU Publications Office, 2024. <https://data.europa.eu/doi/10.2873/34576>.
- . Verordening (EG) nr. 726/2004 van het Europees Parlement en de Raad van 31 maart 2004 tot vaststelling van communautaire procedures voor het verlenen van vergunningen en het toezicht op geneesmiddelen voor menselijk en diergeneeskundig gebruik en tot oprichting van een Europees Geneesmiddelenbureau, Pub. L. No. PB L 136 (2004). <http://data.europa.eu/eli/reg/2004/726/oj>.
- . Verordening (EU) Nr. 536/2014 van 16 april 2014 betreffende klinische proeven met geneesmiddelen voor menselijk gebruik en tot intrekking van Richtlijn 2001/20/EG, Pub. L. No. OJ L 158 (2014). <http://data.europa.eu/eli/reg/2014/536/oj>.
- Ewart, Lorna, Athanasia Apostolou, Skyler A. Briggs, Christopher V. Carman, Jake T. Chaff, Anthony R. Heng, Sushma Jadalannagari, e.a. 'Performance Assessment and Economic Analysis of a Human Liver-Chip for Predictive Toxicology'. *Communications Medicine* 2, nr. 1 (6 december 2022): 154. <https://doi.org/10.1038/s43856-022-00209-1>.
- Farrow, Nigel, Patricia Cmielewski, Juliette Delhove, Nathan Rout-Pitt, Lewis Vaughan, Tim Kuchel, Chris Christou, e.a. 'Towards Human Translation of Lentiviral Airway Gene Delivery for Cystic Fibrosis: A One-Month CFTR and Reporter Gene Study in Marmosets'. *Human Gene Therapy* 32, nr. 15-16 (augustus 2021): 806-16. <https://doi.org/10.1089/hum.2020.267>.
- FDA. 'Nonclinical Considerations for Mitigating Nonhuman Primate Supply Constraints Arising From the COVID-19 Pandemic; Guidance for Industry; Availability'. FDA-2021-D-1311, 24 februari 2022. <https://www.federalregister.gov/documents/2022/02/24/2022-03915/nonclinical-considerations-for-mitigating-nonhuman-primate-supply-constraints-arising-from-the>.
- Ferreira, Guilherme S., Francis M. Dijkstra, Désirée H. Veening-Griffioen, Wouter P. C. Boon, Huub Schellekens, Ellen H. M. Moors, Peter J. K. van Meer, Frederik E. Stuurman, en Joop M. A. van Gerven. 'Translatability of Preclinical to Early Clinical Tolerable and Pharmacologically Active Dose Ranges for Central Nervous System Active Drugs'. *Translational Psychiatry* 13, nr. 1 (1 maart 2023): 1-12. <https://doi.org/10.1038/s41398-023-02353-1>.
- Ferreira, Guilherme S., Désirée H. Veening-Griffioen, Wouter P. C. Boon, Ellen H. M. Moors, Christine C. Gispén-de Wied, Huub Schellekens, en Peter J. K. van Meer. 'A Standardised Framework to Identify Optimal Animal Models for Efficacy Assessment in Drug Development'. *PLOS ONE* 14, nr. 6 (13 juni 2019): e0218014. <https://doi.org/10.1371/journal.pone.0218014>.
- Freriks, A.A., B.M.J. Van der Meulen, H. Van den Belt, H. Ten Holt, en J. Verstappen. 'Noodzakelijk kwaad: Evaluatie van de Wet op dierproeven'. Wageningen, 2005.
- Frey, Jessica, Jackson Cagle, Kara A. Johnson, Joshua K. Wong, Justin D. Hilliard, Christopher R. Butson, Michael S. Okun, en Coralie De Hemptinne. 'Past, Present, and Future of Deep Brain Stimulation: Hardware, Software, Imaging, Physiology and Novel Approaches'. *Frontiers in Neurology* 13 (9 maart 2022): 825178. <https://doi.org/10.3389/fneur.2022.825178>.
- Ganesh, Karuna, Chao Wu, Kevin P. O'Rourke, Bryan C. Szeglin, Youyun Zheng, Charles-Etienne Gabriel Sauv e, Mohammad Adileh, e.a. 'A Rectal Cancer Organoid Platform to Study Individual Responses to Chemoradiation'. *Nature Medicine* 25, nr. 10 (oktober 2019): 1607-14.

- <https://doi.org/10.1038/s41591-019-0584-2>.
- Gardner, John. 'A History of Deep Brain Stimulation: Technological Innovation and the Role of Clinical Assessment Tools'. *Social Studies of Science* 43, nr. 5 (oktober 2013): 707-28. <https://doi.org/10.1177/0306312713483678>.
- Geneesmiddelenwet (2007). <https://wetten.overheid.nl/BWBR0021505/2024-01-01>.
- Genzel, Lisa, Roger Adan, Anton Berns, Jeroen J.J.P. Van Den Beucken, Arjan Blokland, Erik H.W.G.M. Boddeke, Willy M. Bogers, e.a. 'How the COVID-19 Pandemic Highlights the Necessity of Animal Research'. *Current Biology* 30, nr. 18 (september 2020): R1014-18. <https://doi.org/10.1016/j.cub.2020.08.030>.
- Gezondheidsraad. 'WBO-essentiële-begrippen-belicht'. Den Haag, 2017.
- Ghosh, Prasanta K. 'Prospects of Emerging 3D Bioprinting Technologies: Major Technology Components, Technology Developers, and End Users—Part I'. *MGM Journal of Medical Sciences* 11, nr. 2 (april 2024): 331-39. https://doi.org/10.4103/mgmj.mgmj_96_24.
- Giessen, JWB van der, AW van de Giessen, en MAH Braks. 'Emerging zoonoses: Early warning and surveillance in the Netherlands'. Bilthoven: RIVM, 2010. <https://www.rivm.nl/bibliotheek/rapporten/330214002.pdf>.
- Grimm, Herwig, Nikola Biller-Andorno, Thorsten Buch, Maik Dahlhoff, Gail Davies, Christopher R. Cederroth, Otto Maissen, e.a. 'Advancing the 3Rs: Innovation, Implementation, Ethics and Society'. *Frontiers in Veterinary Science* 10 (15 juni 2023). <https://doi.org/10.3389/fvets.2023.1185706>.
- Grimm, Herwig, I Anna S Olsson, en Peter Sandøe. 'Harm–Benefit Analysis – What Is the Added Value? A Review of Alternative Strategies for Weighing Harms and Benefits as Part of the Assessment of Animal Research'. *Laboratory Animals* 53, nr. 1 (1 februari 2019): 17-27. <https://doi.org/10.1177/0023677218783004>.
- Gruen, Lori, en Erika Fleury. 'Animal Welfare, Animal Rights, and a Sanctuary Ethos'. In *Nonhuman Primate Welfare: From History, Science, and Ethics to Practice*, onder redactie van Lauren M. Robinson en Alexander Weiss, 627-41. Cham: Springer International Publishing, 2023. https://doi.org/10.1007/978-3-030-82708-3_26.
- Harding, John D. 'Nonhuman Primates and Translational Research: Progress, Opportunities, and Challenges'. *ILAR Journal* 58, nr. 2 (1 december 2017): 141-50. <https://doi.org/10.1093/ilar/ilx033>.
- Harrell, Andrew W., Kirsty Reid, John Vahle, Frederic Brouta, Mario Beilmann, Graeme Young, Kylie A. Beattie, Jean Pierre Valentin, Shajahan Shaid, en Peter Brinck. 'Endeavours Made by Trade Associations, Pharmaceutical Companies and Regulators in the Replacement, Reduction and Refinement of Animal Experimentation in Safety Testing of Pharmaceuticals'. *Regulatory Toxicology and Pharmacology* 152 (september 2024): 105683. <https://doi.org/10.1016/j.yrtph.2024.105683>.
- Hart, Bert A 't, S Anwar Jagessar, Yolanda S Kap, en Herbert PM Brok. 'Preclinical Models of Multiple Sclerosis in Nonhuman Primates'. *Expert Review of Clinical Immunology* 3, nr. 5 (september 2007): 749-61. <https://doi.org/10.1586/1744666X.3.5.749>.
- Hartung, Thomas, Alexandra Maertens, en Thomas Luechtefeld. 'E-Validation – Unleashing AI for Validation'. *ALTEX - Alternatives to Animal Experimentation* 41, nr. 4 (22 oktober 2024): 567-87. <https://doi.org/10.14573/altex.2409211>.
- Hobson, William. 'Safety Assessment Studies in Nonhuman Primates'. *International Journal of Toxicology* 19, nr. 2 (1 maart 2000): 141-47. <https://doi.org/10.1080/109158100224962>.
- Hoppe, Meagan, Ahmed Habib, Riya Desai, Lincoln Edwards, Chowdari Kodavali, Natalie Sandel Sherry Psy, en Pascal O. Zinn. 'Human Brain Organoid Code of Conduct'. *Frontiers in Molecular Medicine* 3 (23 maart 2023). <https://doi.org/10.3389/fmmed.2023.1143298>.
- Huber, Hillary F., Susan L. Jenkins, Cun Li, en Peter W. Nathanielsz. 'Strength of Nonhuman Primate Studies of Developmental Programming: Review of Sample Sizes, Challenges, and Steps for Future Work'. *Journal of Developmental Origins of Health and Disease* 11, nr. 3 (juni 2020): 297-306. <https://doi.org/10.1017/S2040174419000539>.
- ICH. 'S11 Nonclinical safety testing in support of development of pediatric pharmaceuticals—Guidance for Industry'. Washington, D.C: FDA, 2021.

- <https://www.fda.gov/media/148478/download>.
- Ineichen, Benjamin V., Eva Furrer, Servan L. Grüniger, Wolfgang E. Zürrer, en Malcolm R. Macleod. 'Analysis of Animal-to-Human Translation Shows That Only 5% of Animal-Tested Therapeutic Interventions Obtain Regulatory Approval for Human Applications'. *PLOS Biology* 22, nr. 6 (13 juni 2024): e3002667. <https://doi.org/10.1371/journal.pbio.3002667>.
- Ingber, Donald E. 'Human Organs-on-Chips for Disease Modelling, Drug Development and Personalized Medicine'. *Nature Reviews. Genetics* 23, nr. 8 (augustus 2022): 467-91. <https://doi.org/10.1038/s41576-022-00466-9>.
- IvD Utrecht. 'Humane eindpunten', z.d. <https://ivd-utrecht.nl/nl/voor-dierproeven/humane-eindpunten>.
- Janssen, Peter, Tadashi Isa, Jose Lanciego, Kirk Leech, Nikos Logothetis, Mu-Ming Poo, en Anna S. Mitchell. 'Visualizing advances in the future of primate neuroscience research'. *Current Research in Neurobiology* 4 (1 januari 2023): 100064. <https://doi.org/10.1016/j.crneur.2022.100064>.
- Janssen, Robine, Laura Benito-Zarza, Pim Cleijpool, Marta G. Valverde, Silvia M Mihăilă, Shanna Bastiaan-Net, Johan Garssen, Linette E. M. Willemsen, en Rosalinde Masereeuw. 'Biofabrication Directions in Recapitulating the Immune System-on-a-Chip'. *Advanced Healthcare Materials*, 24 april 2024, 2304569. <https://doi.org/10.1002/adhm.202304569>.
- Jebran, Ahmad-Fawad, Tim Seidler, Malte Tiburcy, Maria Daskalaki, Ingo Kutschka, Buntaro Fujita, Stephan Ensminger, e.a. 'Engineered Heart Muscle Allografts for Heart Repair in Primates and Humans'. *Nature*, 29 januari 2025, 1-9. <https://doi.org/10.1038/s41586-024-08463-0>.
- Jeger-Madiot, Raphaël, Delphine Planas, Isabelle Staropoli, Hippolyte Debarnot, Jérôme Kervevan, Héloïse Mary, Camilla Collina, e.a. 'Modeling memory B cell responses in a lymphoid organ-chip to evaluate mRNA vaccine boosting'. *Journal of Experimental Medicine* 221, nr. 10 (6 september 2024): e20240289. <https://doi.org/10.1084/jem.20240289>.
- Kang, Serah, Eugene C Chen, Helen Cifuentes, Julia Y Co, Gabrielle Cole, Jessica Graham, Rebecca Hsia, e.a. 'Complex in vitro models positioned for impact to drug testing in pharma: a review'. *Biofabrication* 16, nr. 4 (1 oktober 2024): 042006. <https://doi.org/10.1088/1758-5090/ad6933>.
- Kaur, Rimple Jeet, Surjit Singh, Preeti Sidhu, en Pramod Kumar Sharma. 'TGN-1412 and BIA-2474 Trials with Tragic End: Lessons Learnt To Make Clinical Trials Safer'. *Reviews on Recent Clinical Trials* 13, nr. 4 (2018): 252-56. <https://doi.org/10.2174/1574887113666180521093529>.
- Kawasaki, Minae, Takashi Goyama, Yurika Tachibana, Itsuma Nagao, en Yoko M. Ambrosini. 'Farm and Companion Animal Organoid Models in Translational Research: A Powerful Tool to Bridge the Gap Between Mice and Humans'. *Frontiers in Medical Technology* 4 (12 mei 2022): 895379. <https://doi.org/10.3389/fmedt.2022.895379>.
- Kemnitz et al. (2008). *Animal Research in a Global Environment: Meeting the Challenges: Proceedings of the November 2008 International Workshop*. Washington, D.C.: National Academies Press, 2011. <https://doi.org/10.17226/13175>.
- Kim, HanSol, Eun Jo Jang, Narendra V. Sankpal, Madhumita Patel, en Rajkumar Patel. 'Recent Development of Brain Organoids for Biomedical Application'. *Macromolecular Bioscience* 23, nr. 3 (maart 2023): 2200346. <https://doi.org/10.1002/mabi.202200346>.
- KNAW. 'Excellent hersenonderzoek met minder dierproeven. Kansen en uitdagingen voor proefdiervrij onderzoek in de neurowetenschappen'. Amsterdam, 2019.
- . 'Gebruik van niet-humane primaten (NHP) als proefdier. Nut of Noodzaak?' Amsterdam, 2014.
- Knight, Andrew. 'A Critique of the Bateson Review of Research Using Non-Human Primates', 2012.
- Koopman, Gerrit, Tom Verhoeven, Petra Mooij, Roja F. Acar, Thibault Harmand, Laney Flanagan, Jaco Bakker, e.a. 'Imaging the Immune Sequelae of Infection with SARS-CoV-2 in Nonhuman Primates by Using Two Nanobody PET-Tracers'. *Journal of Medical Virology* 96, nr. 10 (2024): e29956. <https://doi.org/10.1002/jmv.29956>.
- Kramer, K., B. Bovenkerk, en K. ten Cate. 'Ontwikkelingen in de academische dierethiek en hun relevantie voor het denken over gebruik van dieren voor wetenschappelijk onderzoek'. Achtergronddocument. Den Haag: NCad, 2024. <https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKewjw8cSR>

- eCIAxV73QIHJY-
DRkQFnoECBQQAQ&url=https%3A%2F%2Fwww.ncadierproevenbeleid.nl%2Fbinaries%2Fncadierproevenbeleid%2Fdocumenten%2Frapport%2F2024%2F9%2F13%2Fbijlage-3-ontwikkelingen-in-de-academische-dierethiek%2FBijlage%2B3_achtergronddocument_Ontwikkelingen%2Bin%2Bde%2Bacademische%2Bdierethiek.pdf&usg=AOvVaw2irMX9X8MINqTV4PsKrON9&opi=89978449.
- Kuhn, Thomas S. *The structure of scientific revolutions*. Chicago: University of Chicago Press, 1962.
- Leenaars, Cathalijn H. C., Carien Kouwenaar, Frans R. Stafleu, André Bleich, Merel Ritskes-Hoitinga, Rob B. M. De Vries, en Franck L. B. Meijboom. 'Animal to Human Translation: A Systematic Scoping Review of Reported Concordance Rates'. *Journal of Translational Medicine* 17, nr. 1 (december 2019): 223. <https://doi.org/10.1186/s12967-019-1976-2>.
- Leung, Chak Ming, Pim De Haan, Kacey Ronaldson-Bouchard, Ge-Ah Kim, Jihoon Ko, Hoon Suk Rho, Zhu Chen, e.a. 'A Guide to the Organ-on-a-Chip'. *Nature Reviews Methods Primers* 2, nr. 1 (12 mei 2022): 33. <https://doi.org/10.1038/s43586-022-00118-6>.
- Liang, Weizheng, Junli He, Chenyu Mao, Chengwei Yu, Qingxue Meng, Jun Xue, Xueliang Wu, Shanliang Li, Yukai Wang, en Hongyang Yi. 'Gene Editing Monkeys: Retrospect and Outlook'. *Frontiers in Cell and Developmental Biology* 10 (2022): 913996. <https://doi.org/10.3389/fcell.2022.913996>.
- Lindl, Toni, Manfred Völkel, en Roman Kolar. 'Animal Experiments in Biomedical Research. An Evaluation of the Clinical Relevance of Approved Animal Experimental Projects: No Evident Implementation in Human Medicine within 10 Years [Article in German]'. *ALTEX - Alternatives to Animal Experimentation* 22, nr. 3 (1 augustus 2005): 143-51.
- Lorach, Henri, Andrea Galvez, Valeria Spagnolo, Felix Martel, Serpil Karakas, Nadine Intering, Molywan Vat, e.a. 'Walking Naturally after Spinal Cord Injury Using a Brain-Spine Interface'. *Nature* 618, nr. 7963 (juni 2023): 126-33. <https://doi.org/10.1038/s41586-023-06094-5>.
- Low, Lucie A., Christine Mummery, Brian R. Berridge, Christopher P. Austin, en Danilo A. Tagle. 'Organs-on-Chips: Into the next Decade'. *Nature Reviews Drug Discovery* 20, nr. 5 (mei 2021): 345-61. <https://doi.org/10.1038/s41573-020-0079-3>.
- Madden, Judith C., Steven J. Enoch, Alicia Paini, en Mark T.D. Cronin. 'A Review of *In Silico* Tools as Alternatives to Animal Testing: Principles, Resources and Applications'. *Alternatives to Laboratory Animals* 48, nr. 4 (juli 2020): 146-72. <https://doi.org/10.1177/0261192920965977>.
- Maharjan, Sushila, Berivan Cecen, en Yu Shrike Zhang. '3D Immunocompetent Organ-on-a-Chip Models'. *Small Methods* 4, nr. 9 (september 2020): 2000235. <https://doi.org/10.1002/smt.202000235>.
- Manook, Miriam, Danae Olaso, Imran Anwar, Isabel DeLaura, Janghoon Yoon, Yeeun Bae, Andrew Barbas, e.a. 'Prolonged xenokidney graft survival in sensitized NHP recipients by expression of multiple human transgenes in a triple knockout pig'. *Science Translational Medicine* 16, nr. 751 (12 juni 2024): eadk6152. <https://doi.org/10.1126/scitranslmed.adk6152>.
- Meer, P. J. K. van, M. Kooijman, J. W. van der Laan, E. H. M. Moors, en H. Schellekens. 'The Value of Non-Human Primates in the Development of Monoclonal Antibodies'. *Nature Biotechnology* 31, nr. 10 (oktober 2013): 882-83. <https://doi.org/10.1038/nbt.2709>.
- Meer, P. J. K. van, Marlous Kooijman, Christine C. Gispens-de Wied, Ellen H.M. Moors, en Huub Schellekens. 'The Ability of Animal Studies to Detect Serious Post Marketing Adverse Events Is Limited'. *Regulatory Toxicology and Pharmacology* 64, nr. 3 (december 2012): 345-49. <https://doi.org/10.1016/j.yrtph.2012.09.002>.
- Mendez, Juan Carlos, Brook A. L. Perry, Rhyanne J. Heppenstall, Stuart Mason, en Anna S. Mitchell. 'Openness about Animal Research Increases Public Support'. *Nature Neuroscience* 25, nr. 4 (april 2022): 401-3. <https://doi.org/10.1038/s41593-022-01039-z>.
- Menon, Ramkumar, Louis J. Muglia, en Lisa Hara Levin. 'Review on new approach methods to gain insight into the fetomaternal interface physiology'. *Frontiers in Medicine* 10 (30 november 2023): 1304002. <https://doi.org/10.3389/fmed.2023.1304002>.
- Michiels van Verduijnen. *Eenige opmerkingen over dierenmishandeling naar aanleiding van de artikelen 254, 350 en 455 van het nieuwe wetboek van strafrecht*. P. Somerwil, 1881.
- Mijnders, M., S. A. Fuchs, en E. E. S. Nieuwenhuis. 'Mogelijke toepassingen van organoïden in de

- geneeskunde'. *Nederlands Tijdschrift voor de Geneeskunde*, 6011, 2021, nr. 165 (2022).
- Minister van OCW. 'Dierproeven', 15 februari 2024. <https://zoek.officielebekendmakingen.nl/kst-32336-152.pdf>.
- . Instellingsbesluit Commissie onderzoek niet-humane primaten, Staatscourant § (2023). <https://zoek.officielebekendmakingen.nl/stcrt-2024-3370.html>.
- . Voortgang onderzoek verdere verlaging proeven op niet-humane primaten (motie Wassenberg c.s.) (2023). https://www.google.com/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwikh_r-5eqIAxUDwAIHHVphEtwQFnoECBQQAQ&url=https%3A%2F%2Fwww.rijksoverheid.nl%2Fbina-ries%2Frijksoverheid%2Fdocumenten%2Fkamerstukken%2F2023%2F07%2F06%2Fvoortgang-onderzoek-verdere-verlaging-proeven-op-niet-humane-primaten-motie-wassenberg-c-s%2Fvoortgang-onderzoek-verdere-verlaging-proeven-op-niet-humane-primaten-motie-wassenberg-c-s.pdf&usq=AOvVaw3l_rdCh2vFo0Q-FhQvCOBI&opi=89978449.
- Minister van VWS. Wetsvoorstel zeggenschap lichaamsmateriaal, Pub. L. No. 35844, 2020-2021 3 (2021).
- Miura, Yuki, Min-Yin Li, Omer Revah, Se-Jin Yoon, Genta Narazaki, en Sergiu P. Paşca. 'Engineering Brain Assembloids to Interrogate Human Neural Circuits'. *Nature Protocols* 17, nr. 1 (januari 2022): 15-35. <https://doi.org/10.1038/s41596-021-00632-z>.
- Munn, Zachary, Micah D. J. Peters, Cindy Stern, Catalin Tufanaru, Alexa McArthur, en Edoardo Aromataris. 'Systematic review or scoping review? Guidance for authors when choosing between a systematic or scoping review approach'. *BMC Medical Research Methodology* 18, nr. 1 (19 november 2018): 143. <https://doi.org/10.1186/s12874-018-0611-x>.
- Naald, Mira van der, Steven A J Chamuleau, Julia M L Menon, Wim De Leeuw, Judith De Haan, Dirk J Duncker, en Kimberley Elaine Wever. 'Preregistration of animal research protocols: development and 3-year overview of preclinicaltrials.eu'. *BMJ Open Science* 6, nr. 1 (16 maart 2022). <https://doi.org/10.1136/bmjos-2021-100259>.
- Nahon, Dennis M., Renée Moerkens, Hande Aydogmus, Bas Lendemeijer, Adriana Martínez-Silgado, Jeroen M. Stein, Milica Dostanić, e.a. 'Standardizing Designed and Emergent Quantitative Features in Microphysiological Systems'. *Nature Biomedical Engineering* 8, nr. 8 (augustus 2024): 941-62. <https://doi.org/10.1038/s41551-024-01236-0>.
- National Academies of Sciences, Engineering, and Medicine. *Nonhuman Primate Models in Biomedical Research: State of the Science and Future Needs*. Onder redactie van Kenneth S. Ramos, Autumn Downey, en Olivia C. Yost. Washington, D.C.: National Academies Press, 2023. <https://doi.org/10.17226/26857>.
- National Primate Research Centers. 'A National Resource for the Scientific Research Community', z.d. <https://www.nprcresearch.org/primate/index.php>.
- NC3R. 'NC3Rs Guidelines: Non-human primate accommodation, care and use'. London: NC3R, 2017.
- . 'The ARRIVE Guidelines 2.0: Updated Guidelines for Reporting Animal Research. Originally Published in PLOS Biology, July 2020.' London, 2020.
- NCad. 'De beschikbaarheid en toegankelijkheid van menselijk weefsel voor biomedisch onderzoek en onderwijs'. Nationaal Comité advies dierproevenbeleid, 2023.
- . 'De projectbeoordeling van fundamenteel wetenschappelijk proefdieronderzoek: is schaden-baten analyse het juiste model?' Ministerie van Landbouw, Natuur en Voedselkwaliteit, 16 september 2024. <https://www.ncadierproevenbeleid.nl/documenten/rapport/2024/9/13/bijlage-4-schadenbaten-analyse-fundamenteel-wetenschappelijk-proefdieronderzoek>.
- . 'Evaluatie van het NCad advies "Transitie naar proefdiervrij onderzoek"', 16 september 2024. <https://www.ncadierproevenbeleid.nl/adviezen-ncad/documenten/rapport/2024/9/13/evaluatie-transitie-advies-1.0-transitie-naar-proefdiervrij-onderzoek>.
- . 'Handreiking Synthesis of Evidence in proefdieronderzoek'. Den Haag: Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2019. <https://www.ncadierproevenbeleid.nl/documenten/brochure/2019/3/26/handreiking-synthesis-of-evidence-in-proefdieronderzoek>.

- . 'Inschatten van Cumulatief Ongerief. Zienswijze van het NCad op verzoek van de Centrale Commissie Dierproeven.', 2022.
- . 'Nationaal Comité advies dierproevenbeleid'. Overheidswebsite, 2024. <https://www.ncadierproevenbeleid.nl/>.
- . 'Streefbeeld voor proefdierlijke innovaties in de immunologie'. Den Haag: Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2024. <https://www.ncadierproevenbeleid.nl/documenten/publicatie/24/3/13/streefbeeld-immunologie>.
- . 'Transitie naar proefdierlijk onderzoek — Over mogelijkheden voor het uitfaseren van dierproeven en het stimuleren van proefdierlijke innovatie'. Den Haag: Nationaal Comité advies dierproevenbeleid, 2016.
- . 'Verslag digitale bijeenkomst CCD/NCad 28-09-2020', 2020. <https://www.ncadierproevenbeleid.nl/documenten/vergaderstuk/2021/6/1/verslag-ncad-ccd-overleg-28-09-2020>.
- . 'Zienswijze: Afwegingskader voor het Prioriteren van Dierproeven voor Vervanging - Publicatie - Nationaal Comité advies dierproevenbeleid'. Ministerie van Landbouw, Natuur en Voedselkwaliteit, 25 juli 2023. <https://www.ncadierproevenbeleid.nl/documenten/publicatie/23/7/25/zienswijze-afwegingskader-voor-het-prioriteren-van-dierproeven-voor-vervanging>.
- Nieuwland, Juliana M., Erik Nutma, Ingrid H. C. H. M. Philippens, Kinga P. Böszörményi, Edmond J. Remarque, Jaco Bakker, Lisette Meijer, e.a. 'Longitudinal Positron Emission Tomography and Postmortem Analysis Reveals Widespread Neuroinflammation in SARS-CoV-2 Infected Rhesus Macaques'. *Journal of Neuroinflammation* 20, nr. 1 (29 juli 2023): 179. <https://doi.org/10.1186/s12974-023-02857-z>.
- NIN. 'Nederlands Herseninstituut - Master the mind', 2024. <https://herseninstituut.nl/>.
- . 'Onderzoek', 21 december 2023. <https://herseninstituut.nl/onderzoeksgroepen/roelfsema/onderzoek/>.
- . 'Roelfsema Group - Visual perception, blindness & plasticity', 2024. <https://nin.nl/research-groups/roelfsema/#publications>.
- Normile, Dennis. 'China Bets Big on Brain Research with Massive Cash Infusion and Openness to Monkey Studies'. *Science*. Geraadpleegd 18 november 2024. <https://www.science.org/content/article/china-bets-big-brain-research-massive-cash-infusion-and-openness-monkey-studies>.
- NVWA. 'Dierproeven voor onderzoek'. Overheidswebsite, 2024. <https://www.nvwa.nl/onderwerpen/dierproeven-voor-onderzoek>.
- . 'Zo doende 2022: Jaaroverzicht dierproeven en proefdieren van de Nederlandse Voedsel- en Warenautoriteit'. Den Haag, 2024.
- OECD. 'Guidelines for the Testing of Chemicals'. OECD. Geraadpleegd 6 november 2024. <https://www.oecd.org/en/topics/sub-issues/testing-of-chemicals/test-guidelines.html>.
- Office fédéral de la sécurité alimentaire et des affaires vétérinaires. 'Expériences sur animaux en 2022 en Suisse', <https://www.tv-statistik.ch/fr/statistique-simples/>.
- Oliver Milman. 'Plan for US "mini-city" of 30,000 monkeys for medical research faces backlash'. *The Guardian*, 16 februari 2024. <https://www.theguardian.com/us-news/2024/feb/16/georgia-monkey-animal-testing-facility>.
- Onesto, Massimo M., Ji-il Kim, en Sergiu P. Pasca. 'Assembloid models of cell-cell interaction to study tissue and disease biology'. *Cell Stem Cell* 31, nr. 11 (7 november 2024): 1563-73. <https://doi.org/10.1016/j.stem.2024.09.017>.
- Passini, Elisa, Oliver J. Britton, Hua Rong Lu, Jutta Rohrbacher, An N. Hermans, David J. Gallacher, Robert J. H. Greig, Alfonso Bueno-Orovio, en Blanca Rodriguez. 'Human In Silico Drug Trials Demonstrate Higher Accuracy than Animal Models in Predicting Clinical Pro-Arrhythmic Cardiotoxicity'. *Frontiers in Physiology* 8 (12 september 2017): 668. <https://doi.org/10.3389/fphys.2017.00668>.
- PDPC. 'Pandemic & Disaster Preparedness Center'. Convergence. Geraadpleegd 29 januari 2025. <https://convergence.nl/nl/pandemic-disaster-preparedness-center/>.

- Philippens, Ingrid H. C. H. M., Kinga P. Böszörményi, Jacqueline A. M. Wubben, Zahra C. Fagrouch, Nikki van Driel, Amber Q. Mayenburg, Diana Lozovagia, e.a. 'Brain Inflammation and Intracellular α -Synuclein Aggregates in Macaques after SARS-CoV-2 Infection'. *Viruses* 14, nr. 4 (8 april 2022): 776. <https://doi.org/10.3390/v14040776>.
- Phillips, Kimberley A., Karen L. Bales, John P. Capitanio, Alan Conley, Paul W. Czoty, Bert A. 'T Hart, William D. Hopkins, e.a. 'Why Primate Models Matter'. *American Journal of Primatology* 76, nr. 9 (september 2014): 801-27. <https://doi.org/10.1002/ajp.22281>.
- Picollet-D'hahan, Nathalie, Agnieszka Zuchowska, Iris Lemeunier, en Séverine Le Gac. 'Multiorgan-on-a-Chip: A Systemic Approach To Model and Decipher Inter-Organ Communication'. *Trends in Biotechnology*, Special Issue: Microphysiological Systems, 39, nr. 8 (1 augustus 2021): 788-810. <https://doi.org/10.1016/j.tibtech.2020.11.014>.
- Portugal-Cohen, Meital, Dror Cohen, Ron Kohen, en Miriam Oron. 'Exploitation of alternative skin models from academia to industry: proposed functional categories to answer needs and regulation demands'. *Frontiers in Physiology* 14 (2 juni 2023): 1215266. <https://doi.org/10.3389/fphys.2023.1215266>.
- Prescott, Mark J. 'Using Primates in Captivity: Research, Conservation, and Education'. In *Nonhuman Primate Welfare: From History, Science, and Ethics to Practice*, onder redactie van Lauren M. Robinson en Alexander Weiss, 57-78. Cham: Springer International Publishing, 2023. https://doi.org/10.1007/978-3-030-82708-3_3.
- Prior, Helen, Paul Baldrick, David O. Clarke, Elisa Passini, Fiona Sewell, en Peter Van Meer. 'Exploring Greater Flexibility for Chronic Toxicity Study Designs to Support Human Safety Assessment While Balancing 3Rs Considerations'. *International Journal of Toxicology* 43, nr. 5 (oktober 2024): 456-63. <https://doi.org/10.1177/10915818241255885>.
- Proefdiervrij. 'Helpathon: help mee proefdiervrije wetenschap te versnellen', z.d. <https://proefdiervrij.nl/actueel/helpathon-utrecht-science-park>.
- Raad voor Dierenaangelegenheden. 'Staat van het Dier 2024'. Den Haag, 2024.
- Rathenau Instituut. 'Ethische overwegingen rond dierproeven spelen meer dan ooit een rol'. Den Haag, 2023. <https://www.rathenau.nl/nl/gezondheid/ethische-overwegingen-rond-dierproeven-spelen-meer-dan-ooit-een-rol>.
- . 'Van Aap naar beter. Een verkenning en dialoog over proeven met apen.' Den Haag, 2017.
- Ravindran, Resmi, Harsharonjit Kang, Cindy McReynolds, Gursharan Kaur Sanghar, W. L. William Chang, Santhamani Ramasamy, Afsal Kolloli, e.a. 'Dynamics of temporal immune responses in nonhuman primates and humans immunized with COVID-19 vaccines'. *PLOS ONE* 18, nr. 10 (19 oktober 2023): e0287377. <https://doi.org/10.1371/journal.pone.0287377>.
- Regan, T. *The Case for Animal Rights*. Berkeley, CA: niversity of California Press, 1983.
- Rekenkamer, Algemene. 'Uit de pandemie. Onderzoek naar de aankoop van vaccins tegen COVID-19'. Den Haag, 2024.
- Rid, Annette, en Meta Roestenberg. 'Judging the Social Value of Controlled Human Infection Studies'. *Bioethics* 34, nr. 8 (2020): 749-63. <https://doi.org/10.1111/bioe.12794>.
- Rider, Patrick, Željka Perić Kačarević, Said Alkildani, Sujith Retnasingh, en Mike Barbeck. 'Bioprinting of Tissue Engineering Scaffolds'. *Journal of Tissue Engineering* 9 (januari 2018): 204173141880209. <https://doi.org/10.1177/2041731418802090>.
- Rilling, James K. 'Human and Nonhuman Primate Brains: Are They Allometrically Scaled Versions of the Same Design?' *Evolutionary Anthropology: Issues, News, and Reviews* 15, nr. 2 (maart 2006): 65-77. <https://doi.org/10.1002/evan.20095>.
- Ritskes-Hoitinga, Merel. 'Medical Regulators: Look beyond Animal Tests'. *Nature* 604, nr. 7907 (27 april 2022): 599-599. <https://doi.org/10.1038/d41586-022-01110-6>.
- Ritskes-Hoitinga, Merel, Yari Barella, en Tineke Kleinhout-Vliek. 'The Promises of Speeding Up: Changes in Requirements for Animal Studies and Alternatives during COVID-19 Vaccine Approval—A Case Study'. *Animals* 12, nr. 13 (5 juli 2022): 1735. <https://doi.org/10.3390/ani12131735>.
- Ritskes-Hoitinga, Merel, Marlies Leenaars, Marc Avey, Maroeska Rovers, en Rob Scholten. 'Systematic Reviews of Preclinical Animal Studies Can Make Significant Contributions to Health Care and More Transparent Translational Medicine'. *Cochrane Database of Systematic*

- Reviews*, nr. 3 (2014). <https://doi.org/10.1002/14651858.ED000078>.
- RIVM. 'Infectieziektenbestrijding', 3 juli 2024. www.rivm.nl/infectieziektebestrijding.
- . 'Landscape New Approach Methodologies (NAMs) Safety Assessment Chemical Substances'. Bilthoven, 2022.
- . 'Landscape New Approach Methodologies (NAMs) safety assessment pharmaceutical products'. Bilthoven, 2022. <https://www.rivm.nl/en/documenten/landscape-new-approach-methodologies-nams-safety-assessment-pharmaceutical-products>.
- . 'Towards the Future of Toxicity Testing. Landscape New Approach Methodologies (NAMs) Safety Assessment Pharmaceutical Products'. Bilthoven, 2024.
- Robinson, Lauren M., en Alexander Weiss, red. *Nonhuman Primate Welfare: From History, Science, and Ethics to Practice*. Cham: Springer International Publishing, 2023. <https://doi.org/10.1007/978-3-030-82708-3>.
- . 'Primate Personality and Welfare'. In *Nonhuman Primate Welfare: From History, Science, and Ethics to Practice*, onder redactie van Lauren M. Robinson en Alexander Weiss, 395-411. Cham: Springer International Publishing, 2023. https://doi.org/10.1007/978-3-030-82708-3_17.
- Rockx, Barry, Thijs Kuiken, Sander Herfst, Theo Bestebroer, Mart M. Lamers, Bas B. Oude Munnink, Dennis de Meulder, e.a. 'Comparative pathogenesis of COVID-19, MERS, and SARS in a nonhuman primate model'. *Science* 368, nr. 6494 (29 mei 2020): 1012-15. <https://doi.org/10.1126/science.abb7314>.
- Roelfsema, Pieter R., en Stefan Treue. 'Basic Neuroscience Research with Nonhuman Primates: A Small but Indispensable Component of Biomedical Research'. *Neuron* 82, nr. 6 (18 juni 2014): 1200-1204. <https://doi.org/10.1016/j.neuron.2014.06.003>.
- Ronaldson-Bouchard, Kacey, Diogo Teles, Keith Yeager, Daniel Naveed Tavakol, Yimu Zhao, Alan Chramiec, Somnath Tagore, e.a. 'A Multi-Organ Chip with Matured Tissue Niches Linked by Vascular Flow'. *Nature Biomedical Engineering* 6, nr. 4 (april 2022): 351-71. <https://doi.org/10.1038/s41551-022-00882-6>.
- Roosen, Geert V. T., Roos van Schuijlenburg, Anneflour D. O. Hensen, Jan Pieter R. Koopman, Olivia A. C. Lamers, Fiona J. A. Geurten, Jeroen C. Sijtsma, e.a. 'Single Immunization with Genetically Attenuated PfΔmei2 (GA2) Parasites by Mosquito Bite in Controlled Human Malaria Infection: A Placebo-Controlled Randomized Trial'. *Nature Medicine* 31, nr. 1 (januari 2025): 218-22. <https://doi.org/10.1038/s41591-024-03347-2>.
- Rots, Nynke en Els, Cécile van. 'Vaccinontwikkeling tijdens een pandemie: snel en toch zorgvuldig | RIVM'. *RIVM Infectieziekten Bulletin*, 14 december 2023. <https://www.rivm.nl/weblog/ib-vaccinontwikkeling-tijdens-pandemie-snel-en-toch-zorgvuldig>.
- Russell, William Moy Stratton, en Rex Leonard Burch. *The principles of humane experimental technique*. Vol. 238. Methuen London, 1959.
- Sasserath, Trevor, John W. Rumsey, Christopher W. McAleer, Lee Richard Bridges, Christopher J. Long, Daniel Elbrecht, Franz Schuler, e.a. 'Differential Monocyte Actuation in a Three-Organ Functional Innate Immune System-on-a-Chip'. *Advanced Science* 7, nr. 13 (juli 2020): 2000323. <https://doi.org/10.1002/advs.202000323>.
- Sato, Kenya, en Erika Sasaki. 'Genetic Engineering in Nonhuman Primates for Human Disease Modeling'. *Journal of Human Genetics* 63, nr. 2 (februari 2018): 125-31. <https://doi.org/10.1038/s10038-017-0351-5>.
- Sauerwein, Robert W., Meta Roestenberg, en Vasee S. Moorthy. 'Experimental Human Challenge Infections Can Accelerate Clinical Malaria Vaccine Development'. *Nature Reviews Immunology* 11, nr. 1 (januari 2011): 57-64. <https://doi.org/10.1038/nri2902>.
- Scanga, Charles A., en JoAnne L. Flynn. 'Modeling Tuberculosis in Nonhuman Primates'. *Cold Spring Harbor Perspectives in Medicine* 4, nr. 12 (12 januari 2014): a018564. <https://doi.org/10.1101/cshperspect.a018564>.
- SCHEER, Scientific Committee on Health Environmental and Emerging Risks. *Final Opinion on the Need for Non-Human Primates in Biomedical Research, Production and Testing of Products and Devices (Update 2017)*. Brussels: EU Publications Office, 2017. <https://data.europa.eu/doi/10.2875/337906>.

- Schmeisser, Sebastian, Andrea Miccoli, Martin Von Bergen, Elisabet Berggren, Albert Braeuning, Wibke Busch, Christian Desaintes, e.a. 'New Approach Methodologies in Human Regulatory Toxicology – Not If, but How and When!' *Environment International* 178 (augustus 2023): 108082. <https://doi.org/10.1016/j.envint.2023.108082>.
- Seyhan, Attila A. 'Lost in translation: the valley of death across preclinical and clinical divide – identification of problems and overcoming obstacles'. *Translational Medicine Communications* 4, nr. 1 (18 november 2019): 18. <https://doi.org/10.1186/s41231-019-0050-7>.
- Shah, Seema K., Franklin G. Miller, Thomas C. Darton, Devan Duenas, Claudia Emerson, Holly Fernandez Lynch, Euzebiusz Jamrozik, e.a. 'Ethics of Controlled Human Infection to Address COVID-19'. *Science* 368, nr. 6493 (22 mei 2020): 832-34. <https://doi.org/10.1126/science.abc1076>.
- Shoji, Jun-ya, Richard P. Davis, Christine L. Mummery, en Stefan Krauss. 'Global Meta-Analysis of Organoid and Organ-on-Chip Research'. *Advanced Healthcare Materials*, 7 augustus 2023, 2301067. <https://doi.org/10.1002/adhm.202301067>.
- Sievers, Sören, Susanne Wieschowski, en Daniel Strech. 'Investigator Brochures for Phase I/II Trials Lack Information on the Robustness of Preclinical Safety Studies'. *British Journal of Clinical Pharmacology* 87, nr. 7 (juli 2021): 2723-31. <https://doi.org/10.1111/bcp.14615>.
- Singer, Peter. *Animal Liberation*. New York: Avon Book, 1975.
- Smidt, H.J. *Geschiedenis van het wetboek van strafrecht: volledige verzameling van regeeringsontwerpen, gewisselde stukken, gevoerde beraadslagingen, enz.* Haarlem: Tjeenk Willink, 1881.
- Solforosi, Laura, Harmjan Kuipers, Mandy Jongeneelen, Sietske K. Rosendahl Huber, Joan E.M. Van Der Lubbe, Liesbeth Dekking, Dominika N. Czapska-Casey, e.a. 'Immunogenicity and Efficacy of One and Two Doses of Ad26.COVS COVID Vaccine in Adult and Aged NHP'. *Journal of Experimental Medicine* 218, nr. 7 (5 juli 2021): e20202756. <https://doi.org/10.1084/jem.20202756>.
- Staatssecretaris van Sociale Zaken en Volksgezondheid. 'Memorie van toelichting - Wijziging van de Wet op de dierproeven', z.d.
- Stokx, Jocelijn. 'Defining Unmet Medical Need'. Gepresenteerd bij EMA Payers Community Meeting, Amsterdam, 2019.
- Swiss Non-Human Primates Competence Center for Research. 'Research at the University of Zürich', z.d. <https://www.unifr.ch/spccr/en/research/projects/unizh.html>.
- 't Hart, Bert A., Jon D. Laman, en Yolanda S. Kap. 'An Unexpected Symbiosis of Animal Welfare and Clinical Relevance in a Refined Nonhuman Primate Model of Human Autoimmune Disease'. In *Nonhuman Primate Welfare: From History, Science, and Ethics to Practice*, onder redactie van Lauren M. Robinson en Alexander Weiss, 605-26. Cham: Springer International Publishing, 2023. https://doi.org/10.1007/978-3-030-82708-3_25.
- Tameris, Michele D, Mark Hatherill, Bernard S Landry, Thomas J Scriba, Margaret Ann Snowden, Stephen Lockhart, Jacqueline E Shea, e.a. 'Safety and Efficacy of MVA85A, a New Tuberculosis Vaccine, in Infants Previously Vaccinated with BCG: A Randomised, Placebo-Controlled Phase 2b Trial'. *The Lancet* 381, nr. 9871 (maart 2013): 1021-28. [https://doi.org/10.1016/S0140-6736\(13\)60177-4](https://doi.org/10.1016/S0140-6736(13)60177-4).
- Tanner, Rachel, Andrew D. White, Charelle Boot, Claudia C. Sombroek, Matthew K. O'Shea, Daniel Wright, Emily Hoogkamer, e.a. 'A Non-Human Primate in Vitro Functional Assay for the Early Evaluation of TB Vaccine Candidates'. *Npj Vaccines* 6, nr. 1 (4 januari 2021): 3. <https://doi.org/10.1038/s41541-020-00263-7>.
- TPI. 'Voortgangsrapportage 2022 programma Transitie Proefdiervrije Innovatie', 30 januari 2023. <https://www.rijksoverheid.nl/documenten/rapporten/2023/01/30/bijlage-1-voortgangsrapportage-2022-programma-transitie-proefdiervrije-innovatie>.
- Treue, Stefan, en Roger Lemon. 'The Indispensable Contribution of Nonhuman Primates to Biomedical Research'. In *Nonhuman Primate Welfare: From History, Science, and Ethics to Practice*, onder redactie van Lauren M. Robinson en Alexander Weiss, 589-603. Cham: Springer International Publishing, 2023. https://doi.org/10.1007/978-3-030-82708-3_24.
- Turner, Patricia V. 'The History of Chimpanzees in Biomedical Research'. In *Nonhuman Primate Welfare: From History, Science, and Ethics to Practice*, onder redactie van Lauren M. Robinson

- en Alexander Weiss, 31-55. Cham: Springer International Publishing, 2023.
https://doi.org/10.1007/978-3-030-82708-3_2.
- Tweede Kamer. Motie van het lid Wassenberg c.s. over een onderzoek naar de mogelijkheid om het aantal proeven op niet-humane primaten verder te verlagen (2022).
<https://www.tweedekamer.nl/kamerstukken/moties/detail?id=2022Z23169&did=2022D49960>.
- UK Home Office. 'Statistics of scientific procedures on living animals, Great Britain: 2022', 9 november 2023. <https://www.gov.uk/government/statistics/statistics-of-scientific-procedures-on-living-animals-great-britain-2022/statistics-of-scientific-procedures-on-living-animals-great-britain-2022>.
- UNESCO. 'UNESCO Recommendation on Open Science'. UNESCO, 2021.
<https://doi.org/10.54677/MNMH8546>.
- Universiteit Utrecht. 'Nationaal Groeifonds investeert 124,5 miljoen euro in transitie naar proefdiervrije innovatie', 15 maart 2024. <https://www.uu.nl/nieuws/nationaal-groeifonds-investeert-1245-miljoen-euro-in-transitie-naar-proefdiervrije-innovatie#:~:text=Nationaal%20Groeifonds%20investeert%20124%2C5%20miljoen%20euro%20in%20transitie%20naar%20proefdiervrije%20innovatie,-15%20maart%202024&text=Het%20Nationaal%20Groeifonds%20investeert%20124,miljoen%20euro%20onder%20voorwaarden%20toegekend>.
- Vasconez Martinez, Mateo Gabriel, Martin Frauenlob, en Mario Rothbauer. 'An Update on Microfluidic Multi-Organ-on-a-Chip Systems for Reproducing Drug Pharmacokinetics: The Current State-of-the-Art'. *Expert Opinion on Drug Metabolism & Toxicology* 20, nr. 6 (juni 2024): 459-71. <https://doi.org/10.1080/17425255.2024.2362183>.
- Veen, Anne Christine van. 'Of Mice, Monkeys, and Better Science: Nonhuman Animal Experimentation and Its Alternatives in the Netherlands (1950-2020)'. Utrecht University, 2021. <https://doi.org/10.33540/726>.
- Veening-Griffioen, Désirée H., Guilherme S. Ferreira, Wouter P. C. Boon, Christine C. Gispens-de Wied, Huub Schellekens, Ellen H. M. Moors, en Peter J. K. Van Meer. 'Tradition, Not Science, Is the Basis of Animal Model Selection in Translational and Applied Research'. *ALTEX* 38, nr. 1 (2021): 49-62. <https://doi.org/10.14573/altex.2003301>.
- Verreck, Frank A. W., Richard A. W. Vervenne, Ivanela Kondova, Klaas W. Van Kralingen, Edmond J. Remarque, Gerco Braskamp, Nicole M. Van Der Werff, e.a. 'MVA.85A Boosting of BCG and an Attenuated, phoP Deficient M. Tuberculosis Vaccine Both Show Protective Efficacy Against Tuberculosis in Rhesus Macaques'. Onder redactie van Niyaz Ahmed. *PLoS ONE* 4, nr. 4 (15 april 2009): e5264. <https://doi.org/10.1371/journal.pone.0005264>.
- Vierboom, Michel P. M., Elia Breedveld, Merel Keehnen, Rianne Klomp, en Jaco Bakker. 'Pain Relief in Nonhuman Primate Models of Arthritis'. In *Inflammation*, onder redactie van Björn E. Clausen en Jon D. Laman, 1559:411-17. New York, NY: Springer New York, 2017.
http://link.springer.com/10.1007/978-1-4939-6786-5_28.
- Vreman, Rick A., Inkatuuli Heikkinen, Ad Schuurman, Claudine Sapede, Jordi Llinares Garcia, Niklas Hedberg, Dimitrios Athanasiou, Jens Grueger, Hubert G. M. Leufkens, en Wim G. Goettsch. 'Unmet Medical Need: An Introduction to Definitions and Stakeholder Perceptions'. *Value in Health: The Journal of the International Society for Pharmacoeconomics and Outcomes Research* 22, nr. 11 (november 2019): 1275-82. <https://doi.org/10.1016/j.jval.2019.07.007>.
- Wang, Shusen, Yuanyuan Du, Boya Zhang, Gaofan Meng, Zewen Liu, Soon Yi Liew, Rui Liang, e.a. 'Transplantation of Chemically Induced Pluripotent Stem-Cell-Derived Islets under Abdominal Anterior Rectus Sheath in a Type 1 Diabetes Patient'. *Cell* 187, nr. 22 (31 oktober 2024): 6152-6164.e18. <https://doi.org/10.1016/j.cell.2024.09.004>.
- Wet Dieren, Nederlandse Staatscourant § (2013). <https://wetten.overheid.nl/BWBR0030250/2024-01-01>.
- Wet medisch-wetenschappelijk onderzoek met mensen (1998).
<https://wetten.overheid.nl/BWBR0009408/2020-01-01>.
- Wet op de Dierproeven (Wod) (2014).
- Wetboek van Strafrecht, art. 254 (1886).

- Wieschowski, Susanne, William Wei Lim Chin, Carole Federico, Sören Sievers, Jonathan Kimmelman, en Daniel Strech. 'Preclinical Efficacy Studies in Investigator Brochures: Do They Enable Risk-Benefit Assessment?' *PLoS Biology* 16, nr. 4 (5 april 2018): e2004879. <https://doi.org/10.1371/journal.pbio.2004879>.
- Wolf, Jayanthi, Samantha Bruno, Michael Eichberg, Risat Jannat, Sharon Rudo, Susan VanRheenen, en Beth-Ann Coller. 'Applying Lessons from the Ebola Vaccine Experience for SARS-CoV-2 and Other Epidemic Pathogens'. *Npj Vaccines* 5, nr. 1 (15 juni 2020): 1-5. <https://doi.org/10.1038/s41541-020-0204-7>.
- Wu, Jiashuo, Ji Li, Yalan He, Junling Huang, Xilong Zhao, Bingyue Pan, Yahui Wang, Liang Cheng, en Junwei Han. 'DrugSim2DR: Systematic Prediction of Drug Functional Similarities in the Context of Specific Disease for Drug Repurposing'. *GigaScience* 12 (28 december 2022): giad104. <https://doi.org/10.1093/gigascience/giad104>.
- ZonMw. 'Kennisagenda Transitie naar Proefdiervrije Innovaties'. Den Haag, 2023.
- . 'Meer kennis met minder dieren: stuwende kracht in de transitie naar proefdiervrije innovaties', januari 2024. <https://www.zonmw.nl/sites/zonmw/files/2024-04/MKMD-Programmatekst-2024-2028-vs9-Final-cover.pdf>.

Appendix 1 Review of international scientific literature

At the committee's request, Dr. James Gallant, Senior Researcher at Leiden University Medical Centre, performed a bibliographic analysis of international literature on NHP research.

The purpose of the study was to perform an exploratory, quantitative analysis of the international context of Dutch NHP research. The limited nature of the resources and time window available meant that the work was necessarily exploratory and subject to certain unavoidable limitations, as described below. The committee believes that the results presented here as an appendix to the report are nevertheless valuable insofar as they complement the qualitative picture that the committee has painted on the basis of its own literature review and expert interviews, and they provide insight into the international context in which Dutch NHP research takes place, which would otherwise have been lacking.

The analysis is limited both in practical and theoretical ways. If the available time and resources had not been subject to practical limitations, it would have been possible to search a greater number of literature databases, including more expensive databases, and to use additional search terms. The first theoretical limitation that applies is that an analysis of scientific publications inevitably includes only NHP research that has been published in scientific journals; it excludes most of the research carried out by the pharmaceutical industry, which is typically reported only within product registration files or in preparation for clinical studies and therefore not findable by means of a PubMed search. Consequently, while it does provide an impression of the international scientific research landscape, this bibliographical analysis does not cover all NHP research. The second theoretical limitation is that the bibliographical analysis provides an exclusively quantitative picture, without any substantive assessment of the publications involved. If a publication is included in PubMed, it may be assumed to be of a certain quality, but its inclusion tells us nothing about its scientific and social impact. Hence, while this bibliographical analysis provides an impression of the scientific effort being devoted to NHP research internationally, it does not shed light on the scientific and social relevance of the research, or on its influence on medicine development or public health. The third theoretical limitation is common to all quantitative scientific research. Numbers can only say so much: 'negative' results are sometimes not published at all, and there are differences in publishing behaviour from one scientific discipline or sub-discipline to another, with the consequence that different publications present results in different ways.

PubMed is one of the largest international databases of medical scientific publications, and the researcher had relatively good access to PubMed. PubMed therefore served as the basis for the bibliographical analysis. Using the search term 'non-human primate*', 14,000 articles were identified. Certain types of publication were then excluded from the analysis: reviews, editorials, systematic reviews, meta-analyses, errata and comments. All such 'publications about publications' were excluded because we wished the analysis to be limited to literature reporting on NHP research.²⁵²

²⁵² Systematic reviews in particular did, of course, play an important role in the committee's investigations (see the report's reference list).

The list of articles remaining after exclusion of those publication types was then 'cleaned up' in various ways; for details, see Gallant's study below. That ultimately left 4,224 complete articles and 763 summaries. Artificial intelligence was then used to seek answers to the committee's questions from the included publications. The questions and the list of included publications can be found on the interactive website: https://provision.shinyapps.io/nhp_tabel. Visitors to the website can filter the research results on the basis of, for example, the research country or time period.

Bibliographical literature analysis by Dr. James Gallant, LUMC

Data collection

In order to answer the committee's questions, we consulted PubMed using the search term '**non-human primate***'.²⁵³ Use of that search term should return all publications that contain the phrase "non-human primate" or "non-human primates". A total of roughly 14,000 articles were identified.

Of the 14,000 identified scientific articles, some, such as editorials and reviews, were not relevant to our research question. Publications of the following types were accordingly excluded from our analysis:

1. Review
2. Editorial
3. Systematic review
4. Meta-analysis
5. Published erratum
6. Comment
7. Retracted publication

Because the analysis focuses on academic publications, it has an inbuilt bias towards NHP research for academic purposes. Non-academic NHP research, such as that undertaken by the pharmaceutical industry, is less likely to be published. It is not therefore reflected in our analysis.

AI prompts

Questions put to the AI software have to be formulated very precisely, in the form of so-called 'prompts'. Presented below is a list of all the elements used to describe the publications in the database – their definitions, whether they were AI-generated, and their prompts.

Column	Column definition	AI	Prompt
ID	PubMed ID	No	N/a
source	Is the source a PDF or an abstract?	No	N/a
primate_institute	Known primate institute	No	N/a
primate_institute_nl	Is the known primate institute based in the Netherlands?	No	N/a
primary_author	Last author of the manuscript	No	N/a

²⁵³ The pronouns 'we' and 'our' are used to emphasise that the key choices regarding the design and implementation of the research were made in consultation with the committee.

Column	Column definition	AI	Prompt
primary_author_country	Country where the primary author is located.	No	N/a
funder_agency	Funder of the research.	No	N/a
funder_country	Country that funded the research.	No	N/a
research_disease	Was the research conducted on a disease?	Yes	If the research was conducted on a disease, which disease was it? If not, return 'unknown'. Examples include COVID, tuberculosis, cardiomyopathy and so forth.
research_major_focus	The major topic of the research; the topics are: applied, fundamental, toxicological, fundamental, behavioural and clinical.	Yes	Classify the research done on the primates as either applied, fundamental, toxicological or behavioural. Examples of applied research are clinical research such as surgical or transplant-based studies. Fundamental would include all laboratory-based research, while toxicological would include pre-clinical studies that test the toxicity of compounds using the primates. Behavioural studies include all social and cognitive-based studies. Return 'unknown' if the answer is not known.
research_minor_focus	What specific field did the research focus on?	Yes	What type of research required the use of the non-human primates? Examples include vaccine, infectious disease, xenotransplantation, social, neurological, metabolic, cardiovascular, reproductive, immunological, diagnosis, drug safety etcetera. This is not an exhaustive list. Refer to the result of research_major_focus to help decide what type of research is described in the text.
research_specific_focus	What was the specific topic of the research?	Yes	What disease or social behaviour was specifically studied using the primates? Return only the name of the disease or behavioural/social trait. An example would be COVID-19 for a research_minor_focus of 'vaccine' or

Column	Column definition	AI	Prompt
			'infectious disease', or Parkinson's for a research_minor_focus of 'neurological'. Those are just examples, not an exhaustive list.
country	Country where the research took place	Yes	In which country was the primate research done? Provide only the country where the primate research institute is located. If it is not known, return 'unknown'.
ethics_institute	Which institute provided ethical clearance for the study?	Yes	Which institute or university provided the ethical clearance for this study? If it is not known, return 'unknown'.
ethics_institute_country	Which country gave ethical clearance for the study?	Yes	Which country provided ethical clearance for this study; in other words, where was the institute or university that provided the ethical clearance located? If it is not known, return 'unknown'.
ethics_protocol	Which guidelines were used or followed to obtain ethical clearance for the study?	Yes	Which guidelines were used to approve the ethical use of the primates? Examples of such guidelines are: AAALAC, IACUC, Directive 2010/63/EU, the Animal Welfare Act (AWA), CCAC guidelines, NC3Rs guidelines, IPS Guidelines, WHO guidelines and so forth. If it is not known, return 'unknown'.
highlight	What was the primary or most important finding of the study?	Yes	Provide a concise summary of the authors' findings that is easily understandable for a layman.
is_review	Is it a review? Not all reviews are registered as reviews in the article metadata.	Yes	Is this study a literature review? Return 'TRUE' or 'FALSE'.
prc	Primate centre where the research was conducted.	Yes	Provide the name of the institute where the primate research was done, if applicable. This might be in the method section of the text and might be prefaced with text along the lines of 'primates were housed...', 'monkeys were housed...'. If it is not known, return 'unknown'.

Column	Column definition	AI	Prompt
prim_outcome	What was the primary outcome of the study; did they achieve what they would like to achieve with the primate research?	Yes	What was the primary outcome of the study?
primate_alt	Was another animal suggested as an alternative to primate research?	Yes	Do the authors propose alternative animals or models to non-human primate research; if so which alternatives? Give short answers like 'mouse', 'rabbit', 'cell line' etcetera. If it is not known or nothing was proposed, return 'unknown'.
primate_comfort	Did the authors state or actively follow guidelines to reduce the discomfort for the animals during the study?	Yes	Do the authors state how the primates were housed, and were they housed comfortably? If so, return the methods used to ensure primate comfort. The answer must be specific to the primates only.
primate_harm	Were the primates harmed in any way during the study?	Yes	Were the primates harmed in this study; if they were harmed in any way, how were they harmed? Primates are considered harmed if they were sacrificed for the study, infected, probed, subjected to surgery, received transplants, injected, had their tissue harvested, killed and so forth. Provide one-word answers such as 'surgery', 'sacrificed', 'emotional', 'infected', 'implant', 'transplant' and so forth. If they were not harmed, return 'no'.
primate_harm_grade	How badly were the primates harmed: not at all, light harm, medium harm or severe harm?	Yes	Provide a grade of harm: light harm, medium harm and severe harm. Examples of light harm would be non-invasive procedures or procedures that induce minimal discomfort, like injections, mild shocks and so forth. Medium harm includes harm that has longer-term effects, such as surgery, infection and so forth. Severe harm includes severe maiming or procedures that result in the death or

Column	Column definition	AI	Prompt
			sacrifice of the primate. If there was no harm done, return 'no harm'.
primate_n	Number of primates used, as reported by the authors.	Yes	How many primates were used in this study? Return a numeric value. If it is not known, return 'unknown'.
primate_used	Did the authors use primates in this study?	Yes	Were primates directly used in this study? To determine whether or not they were used, refer to the methods section of the input text. If there is a section describing animal husbandry specifically associated with monkeys or primates, then primates were used. If primates were used, return 'yes'; otherwise return 'no'.
reason_for_primate_use	Why did the authors choose to use primates?	Yes	Why were primates used in this study? What was the reason for their inclusion, and could an alternative be used? Be concise and provide a one-sentence answer.
species_common	The common name of the primate species.	Yes	What is the common name of the species used in this research? If it is not known, return 'unknown'.
species_scientific	The scientific name of the primate species.	Yes	What was the genus and species of the primate that was used in this research? If it is not known, return 'unknown'.

We used OpenAI's GPT-4 turbo model to assess the PDFs and abstracts and obtain answers to the questions set out above. The GPT-4 turbo model performs the task with a precision of 86 per cent, which, according to the OpenAI benchmark, is better than comparable software.

Corpus of publications for analysis

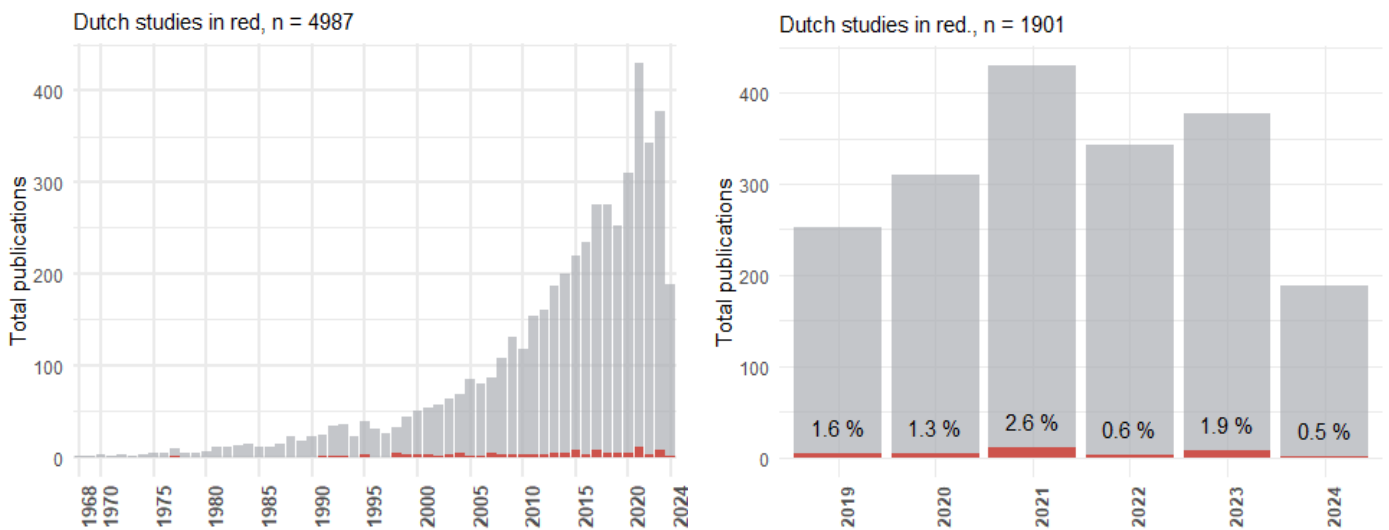
We retained a total of **11,401** manuscripts that described research, of which **8,454** were articles that were not reviews and did report original NHP research. From those, we removed the articles that did not concern animal experiments and those that related to great apes. Hence, we ultimately used **4,224** articles and **763** abstracts.

Number of articles about NHP research per year

The number of articles relating to the use of NHPs serves as an indication of current trends in NHP research, globally and in the Netherlands. Those trends are described in the following graphs on the basis of both the abstracts and the PDFs.

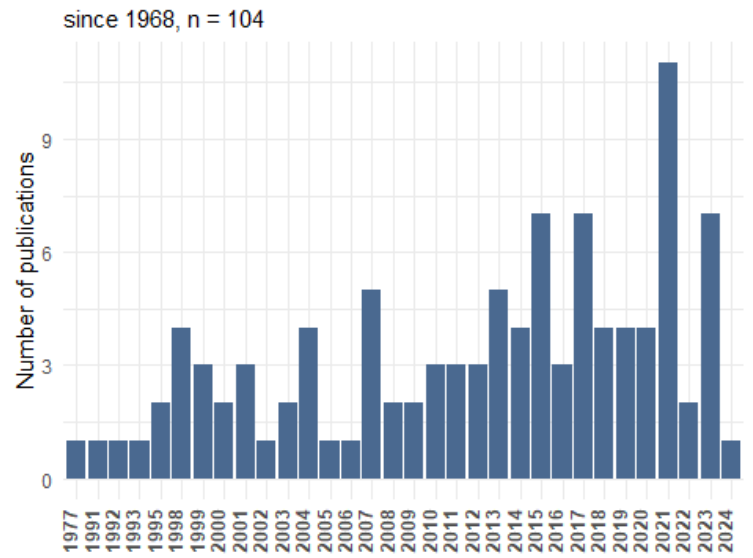
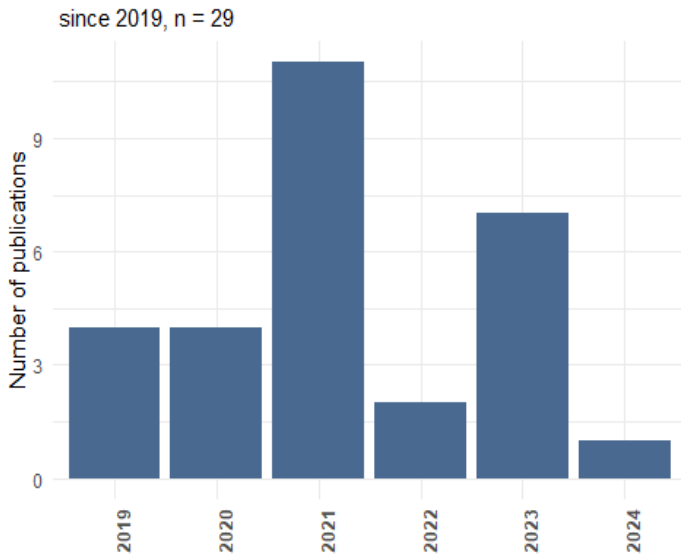
We consider the roles that all countries play in NHP research, but pay special attention to the Netherlands. We begin by collecting the data we require for the visualisation. Two datasets are available to us for assessing the trends in annual NHP research: one lists all the NHP studies performed each year, while the other lists the number of studies carried out in the Netherlands each year and the percentage of all the studies carried out that year accounted for by the Dutch studies. In that context, studies done by Dutch researchers but outside the Netherlands do not count. The data shows an upward trend in the amount of NHP research carried out globally. The Netherlands plays a significant role: the highest percentage of all NHP research accounted for by the Netherlands was 2.6 per cent in 2021.

Filters: primate_used == "yes" & is_review == "FALSE" & primate_harm_grade != "no harm" & primate_harm_grade != "unknown"



A total of 104 published studies were carried out in the Netherlands, of which 29 were published in 2019 or thereafter. As previously indicated, that is an underestimate of the total number of Dutch NHP studies, because not all studies are published, we have looked only at publications listed by PubMed, and we used a limited number of search terms. That is the case for all countries. The number of published Dutch NHP studies increased when the BPRC was founded. The last five years have been reasonably stable, except for a peak that is very probably attributable to the SARS-CoV-2 pandemic.

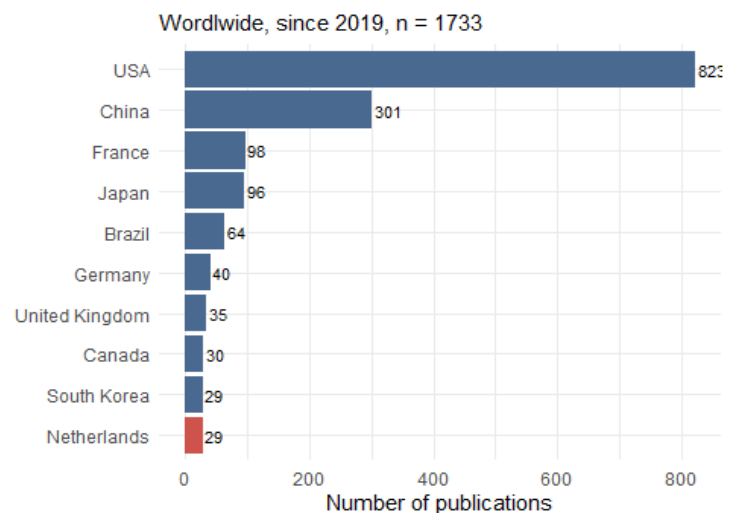
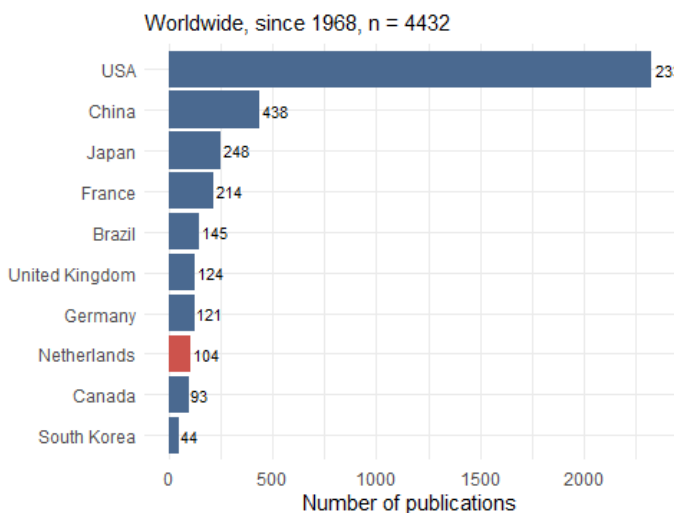
Filters: primate_used == "yes" & is_review == "FALSE" & primate_harm_grade != "no harm" & primate_harm_grade != "unknown"

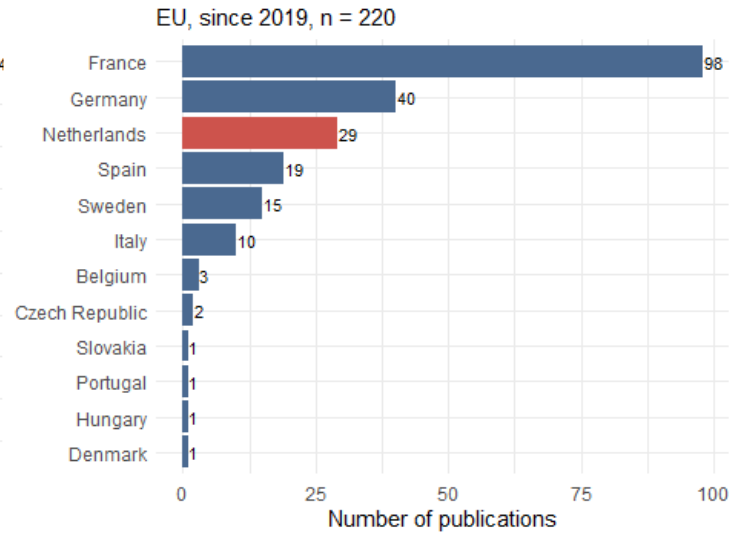
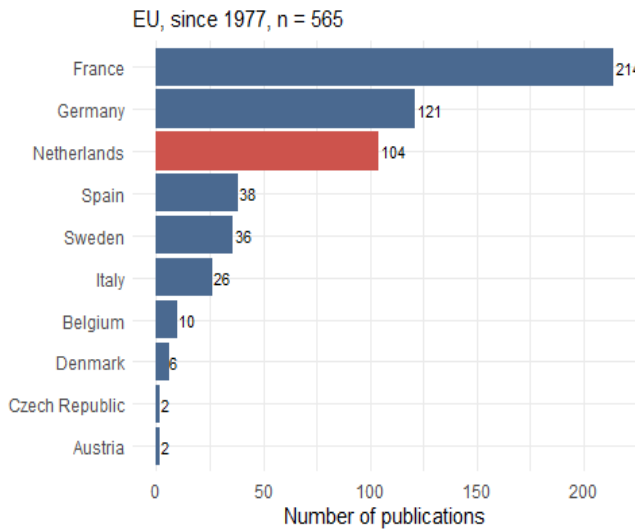


Countries where the most NHP studies are carried out

The volumes of NHP studies carried out in the various countries were compared after excluding all studies whose host country was unknown. We looked at articles that stated that the NHP research was carried out in a particular country, since 1986 and since 2019. In this cohort, 1968 is our earliest date, while 2019 to 2024 reflects recent trends. The Netherlands is in eighth and ninth place in the lists, indicating that the volume of NHP research carried out in the Netherlands is relatively steady as a percentage of the global total.

Filters: primate_used == "yes" & is_review == "FALSE" & primate_harm_grade != "no harm" & primate_harm_grade != "unknown" & country != unknown

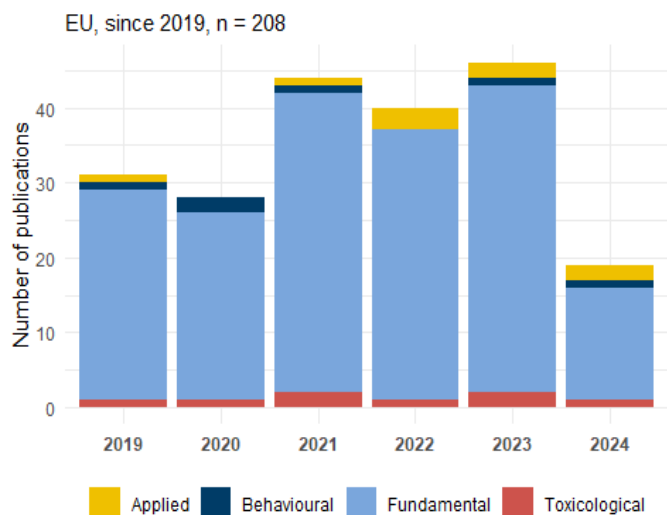
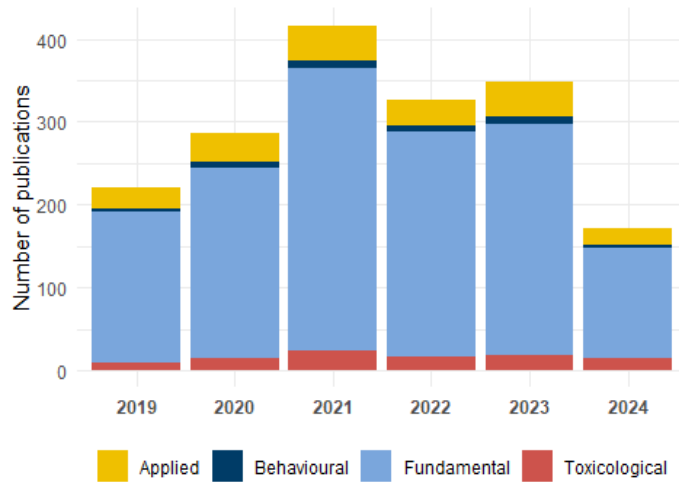


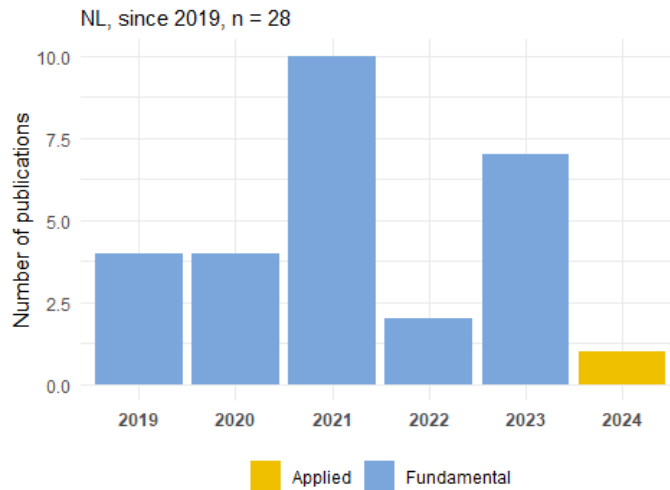


What purposes were NHPs used for in the last six years?

We distinguish the following types of research: basic, toxicological, applied and behavioural. Basic research is the type of research most frequently carried out using NHPs.

Filters: primate_used == "yes" & is_review == "FALSE" & primate_harm_grade != "no harm" & primate_harm_grade != "unknown" & source == "pdf" & Research_major_focus != "unknown" worldwide, since 2019, n = 1771

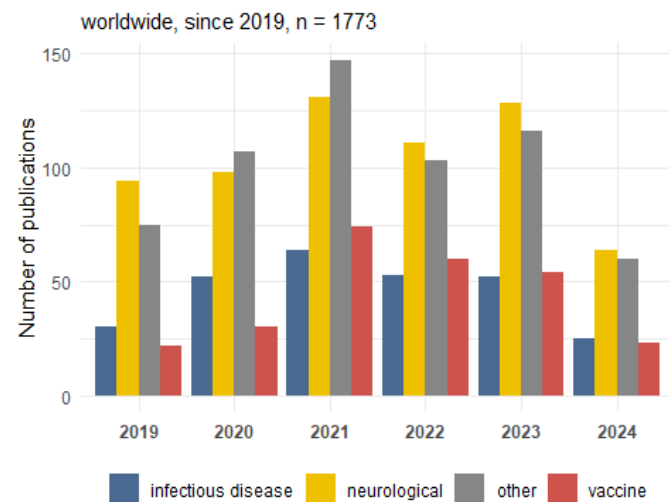
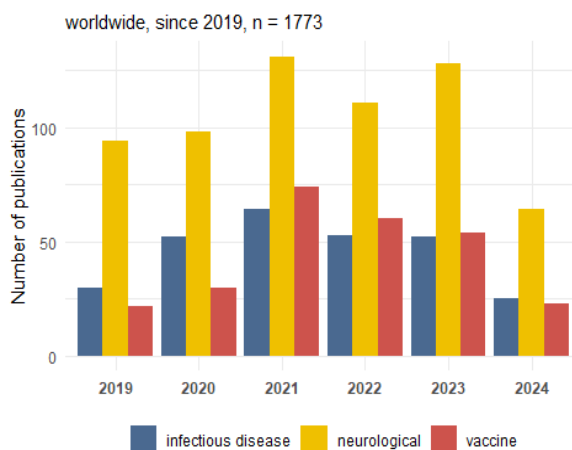




Main disciplines globally

Since 2019, the global focus has been mainly on neurological conditions, infectious diseases and vaccines. Neurological studies are probably as prominent as they are because NHPs are often seen as the best organisms for modelling neurological conditions such as Alzheimer’s disease and Parkinson’s disease. NHPs are also used to study infectious diseases, but less often than other animal models, such as mice; NHP research is often the final preclinical step. In the right-hand graph below, ‘other research’ (grey) includes all other research fields, of which there was a total of seventy-one.

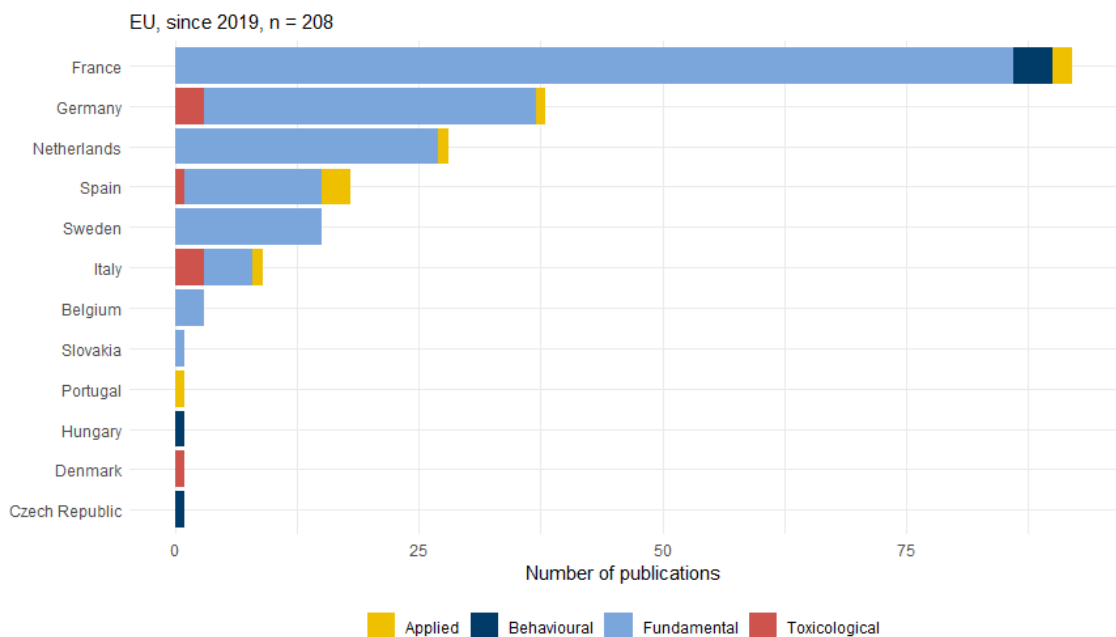
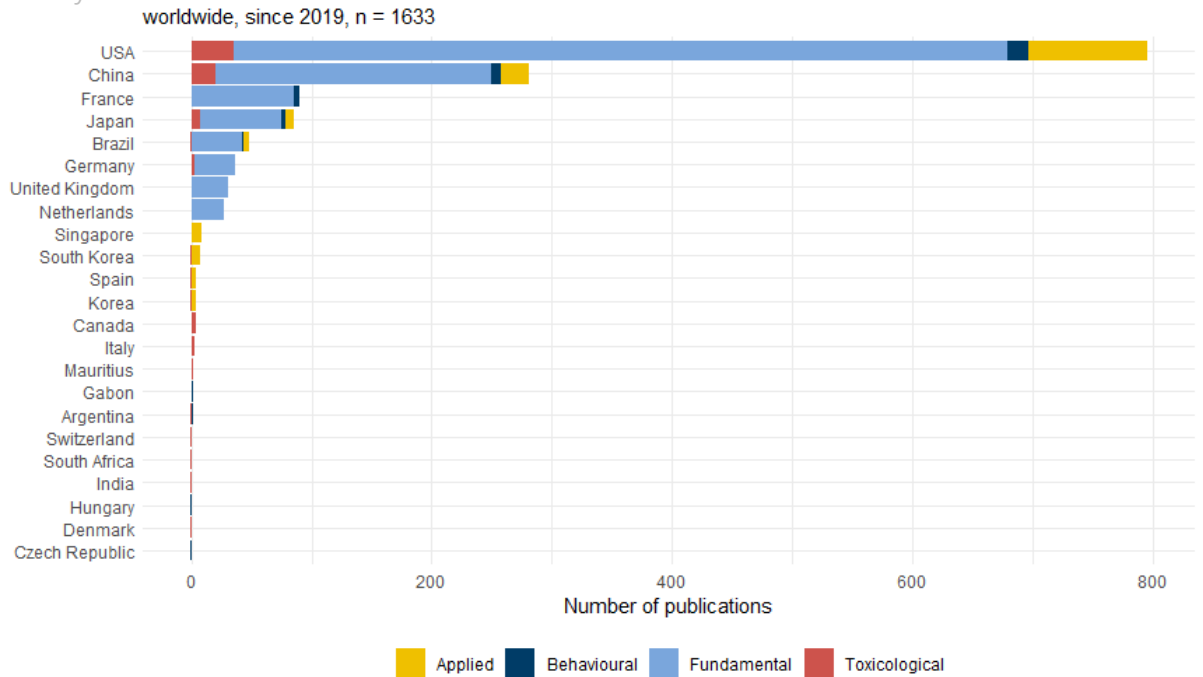
Filters: primate_used == “yes” & is_review == “FALSE” & primate_harm_grade != “no harm” & primate_harm_grade != “unknown” & source == “pdf” & Research_major_focus != “unknown”



Type of primate research by country

We can rank countries on the basis of the type of research and the number of publications that primate centres have produced concerning the relevant type. Where almost all countries, including the Netherlands, are concerned, most of the publications in the PubMed database relate to basic research. The second most common research type is behavioural research. According to our PubMed analysis, the Netherlands is one of the ten most productive countries in the field of NHP research.

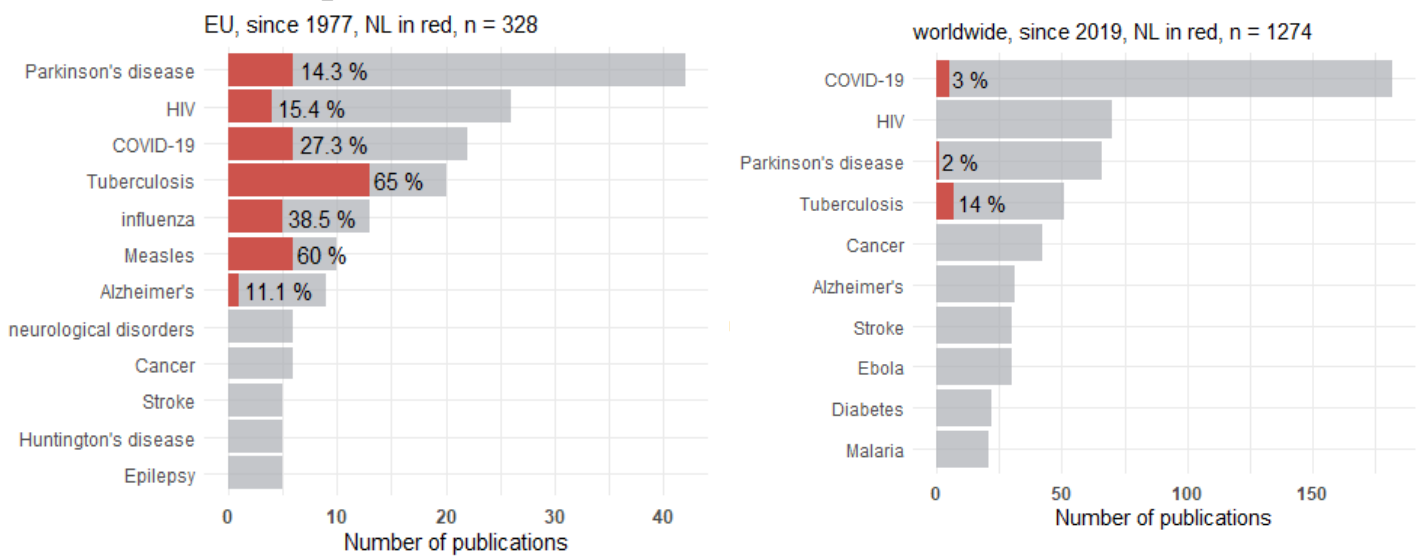
Filters: primate_used == "yes" & is_review == "FALSE" & primate_harm_grade != "no harm" & primate_harm_grade != "unknown" & source == "pdf" & Research_major_focus != "unknown" & country != "unknown"



What pathologies are studied by means of NHP research?

In the NHP publications in PubMed, Parkinson's disease is the most closely studied pathology. NHPs form one of the main models for investigating Parkinson's. From 2019 to 2024, however, SARS-CoV-2 research was dominant. The Netherlands has a strong focus on tuberculosis research, accounting for 13 per cent of all such research conducted globally since 1968 and 14 per cent since 2019. Moreover, the Netherlands was involved in 65 per cent of all PubMed-listed tuberculosis research conducted in the EU, and in 70 per cent since 2019. Tuberculosis is the world's most deadly infectious disease, which is caused by a single bacterium that induces considerable morbidity and increasingly exhibits problematic antibiotic resistance. As a communicable disease, particularly in densely populated regions, tuberculosis remains a potential threat to public health.

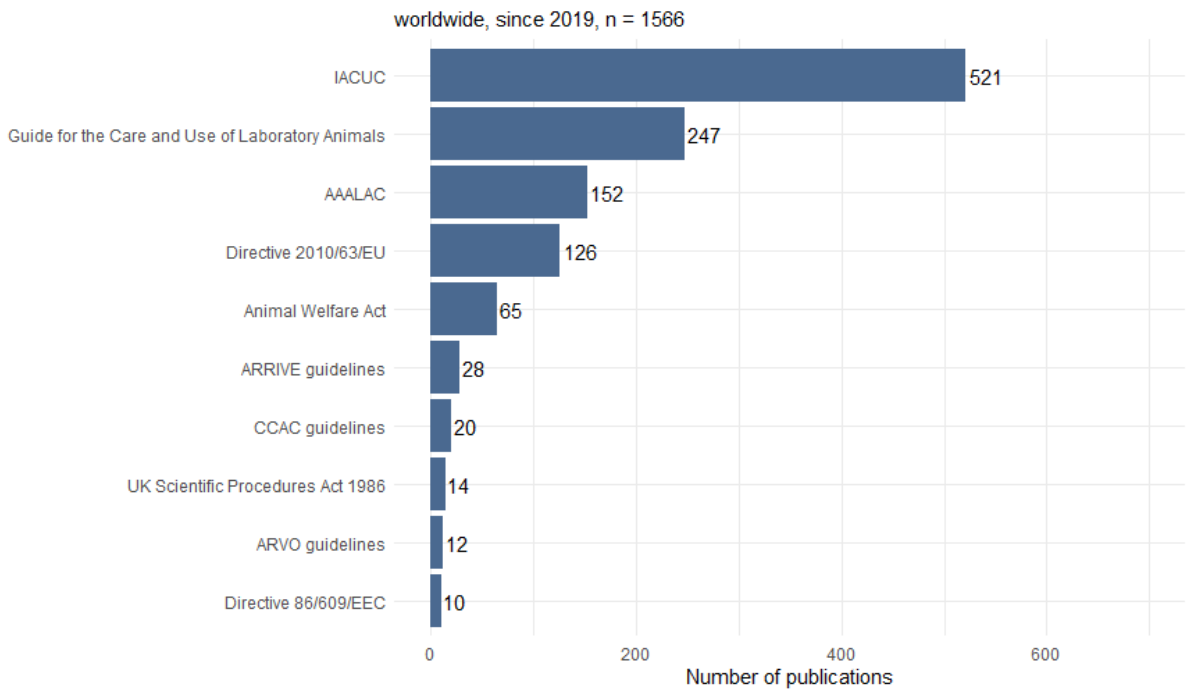
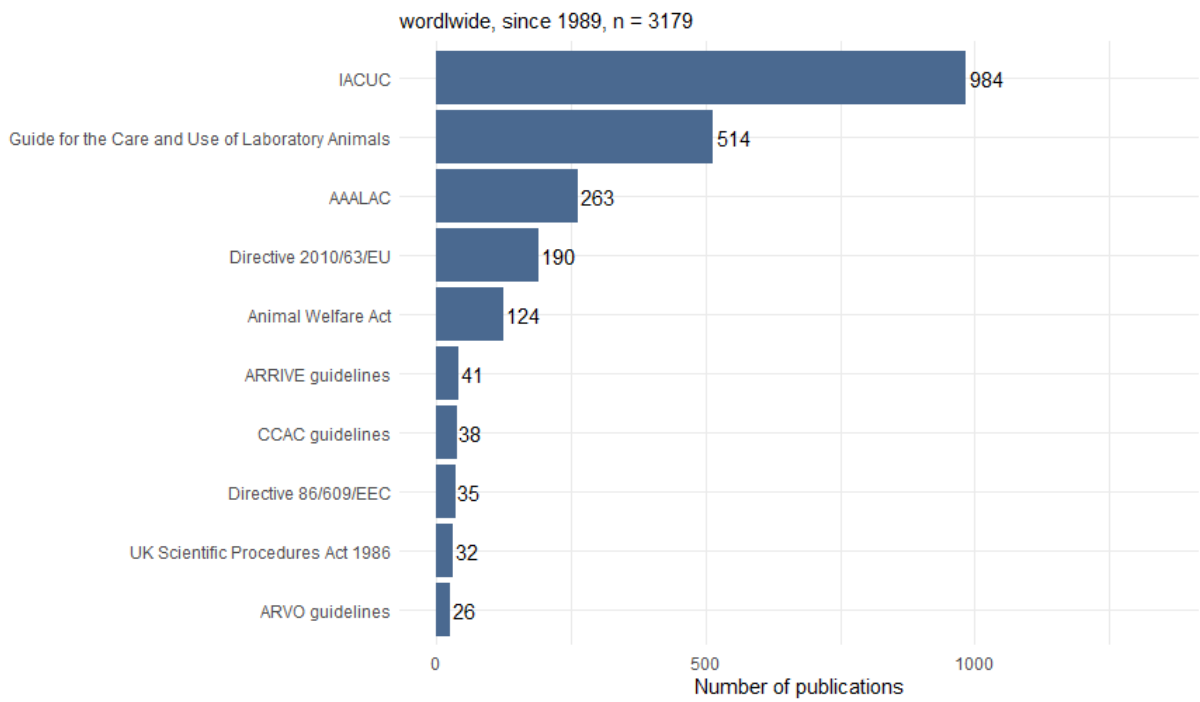
Filters: primate_used == "yes" & is_review == "FALSE" & primate_harm_grade != "no harm" & primate_harm_grade != "unknown" & primate_harm_grade != "unknown" & source == "pdf" & Research_disease != "unknown"

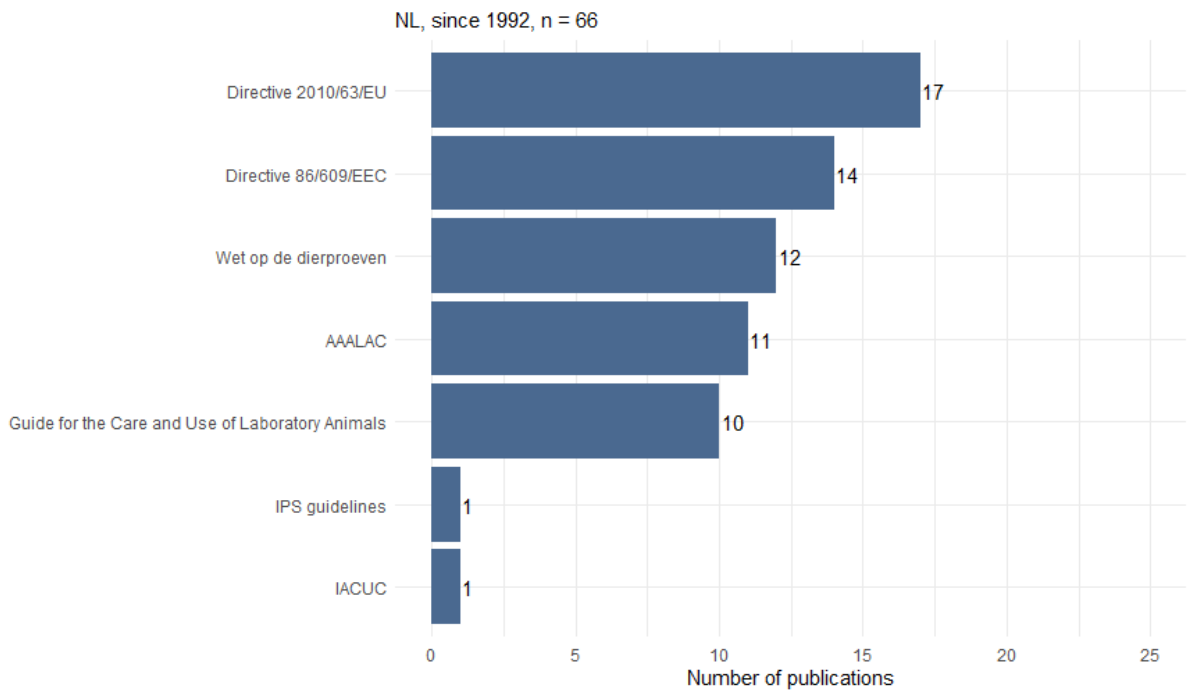
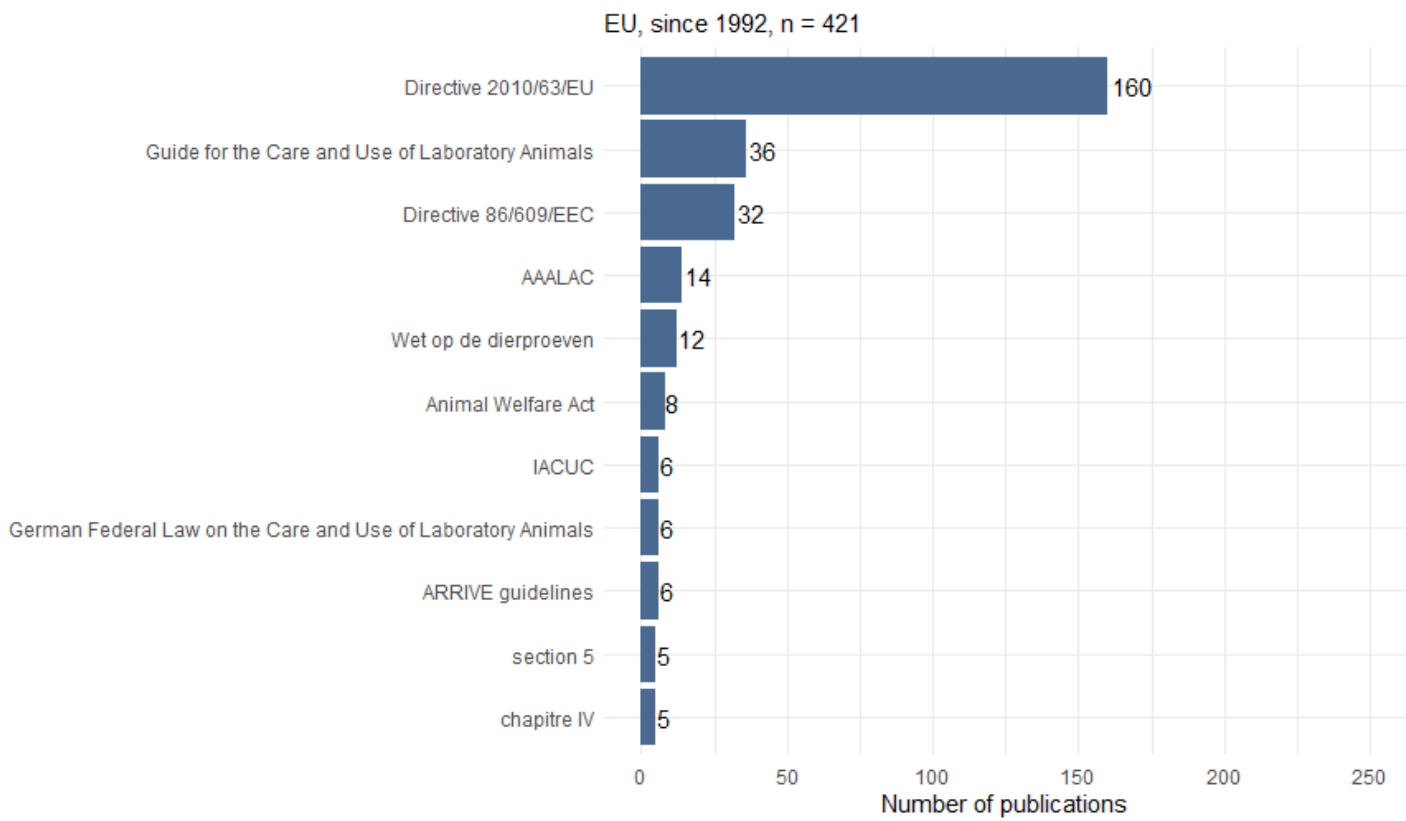


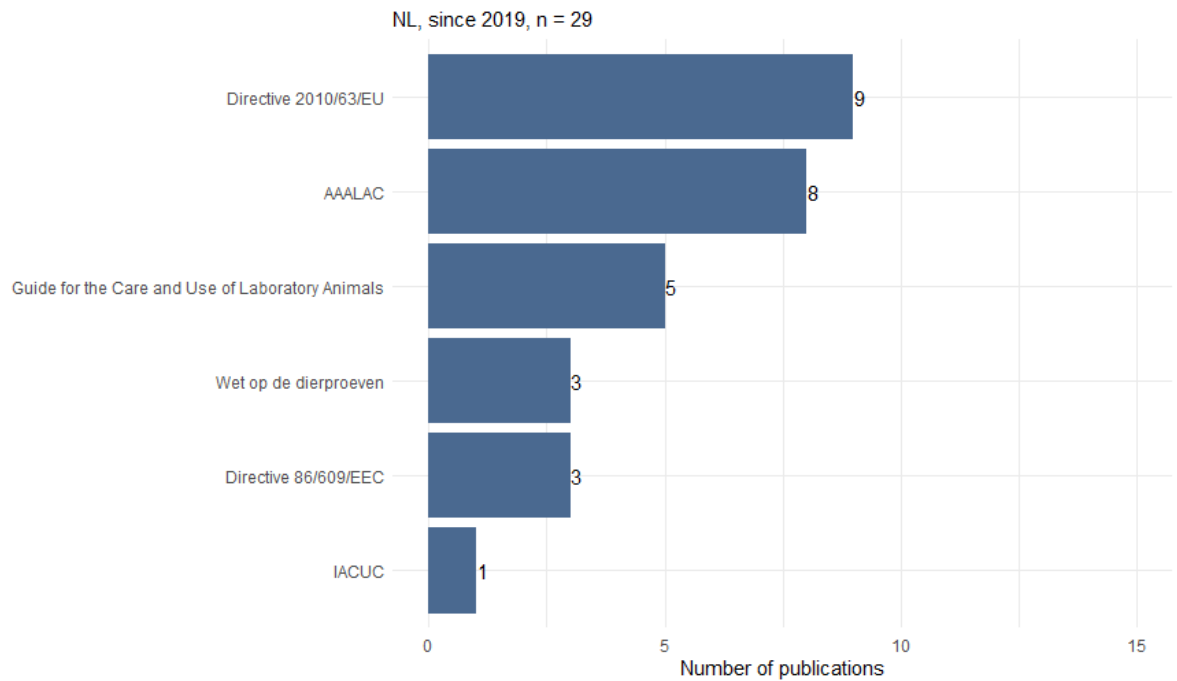
What forms of ethical review are carried out for the licensing of NHP research?

Not all scientific articles indicate what form of ethical review was conducted. However, in some cases, the guidelines followed and those used by the relevant ethical review body are named. The guidelines that must be used can vary from country to country.

Filters: primate_used == yes & is_review == "FALSE" & primate_harm_grade != "no harm" & primate_harm_grade != "unknown" & source == pdf & country != unknown & ethics_protocol != unknown







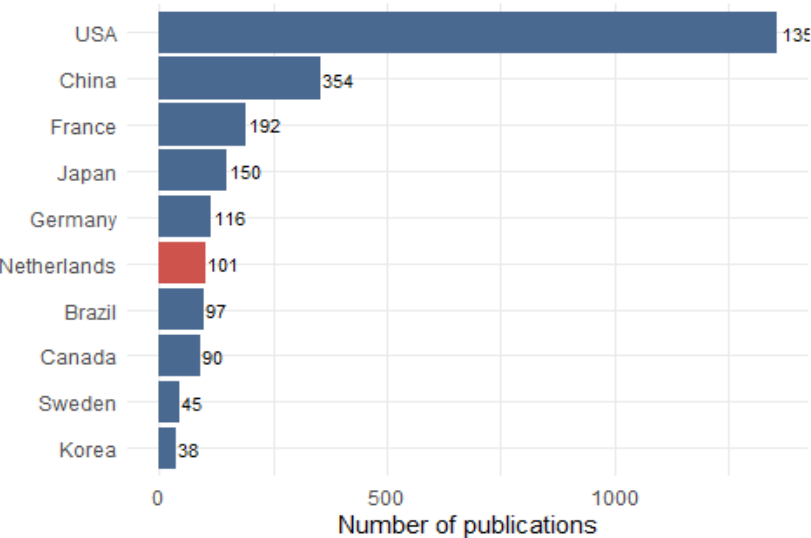
Which researchers use NHPs for research?

An article's last-named author is usually the person with ultimate responsibility for the reported study. We use the last-named author's country as a proxy for the country responsible for the research initiative. That enables us to identify the countries that are most productive in terms of starting NHP research. If an author has more than one affiliation, both countries are counted. Whereas the earlier graphs show where research was actually carried out, the graphs below show the country in which the author who initiated the research was based.

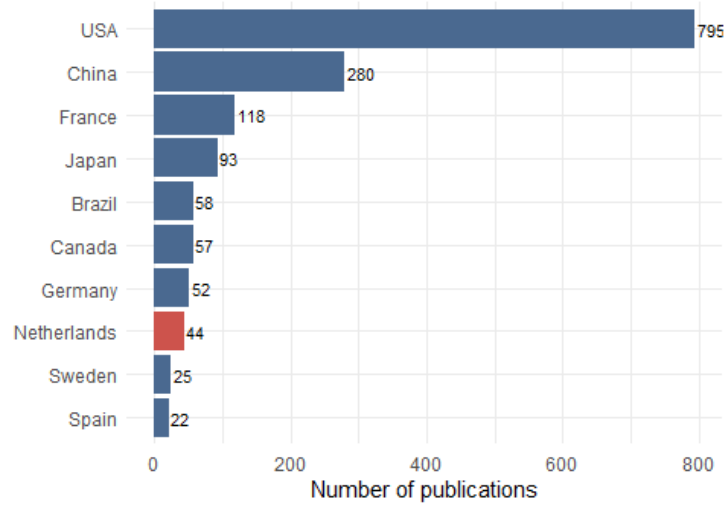
According to the PubMed publication data, the Netherlands is one of the world's ten most active initiators of NHP research, and the EU's third most active. The graphs below are consistent with the earlier graph showing the countries that carry out NHP research. That was to be expected, because most researchers seek to do their research in their own countries. However, some researchers do conduct research in countries other than their own.

Filters: primate_used == "yes" & is_review == "FALSE" & primate_harm_grade != "no harm" & primate_harm_grade != "unknown" & primary_author != "" & primary_author != unknown & primary_author_country != ""

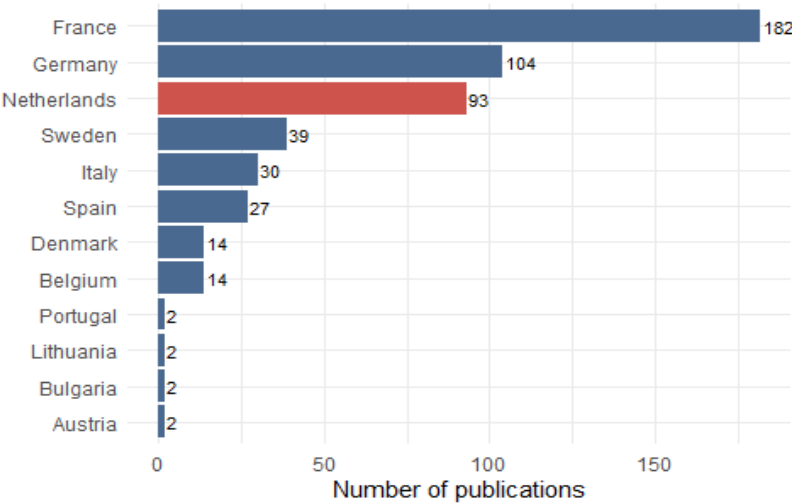
worldwide, since 1987, n = 2943



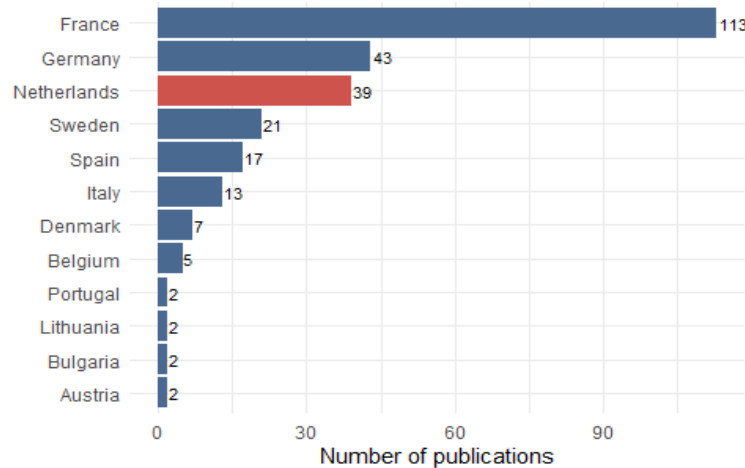
worldwide, since 2019, n = 1772



EU, since 2003, n = 514



EU, since 2019, n = 268

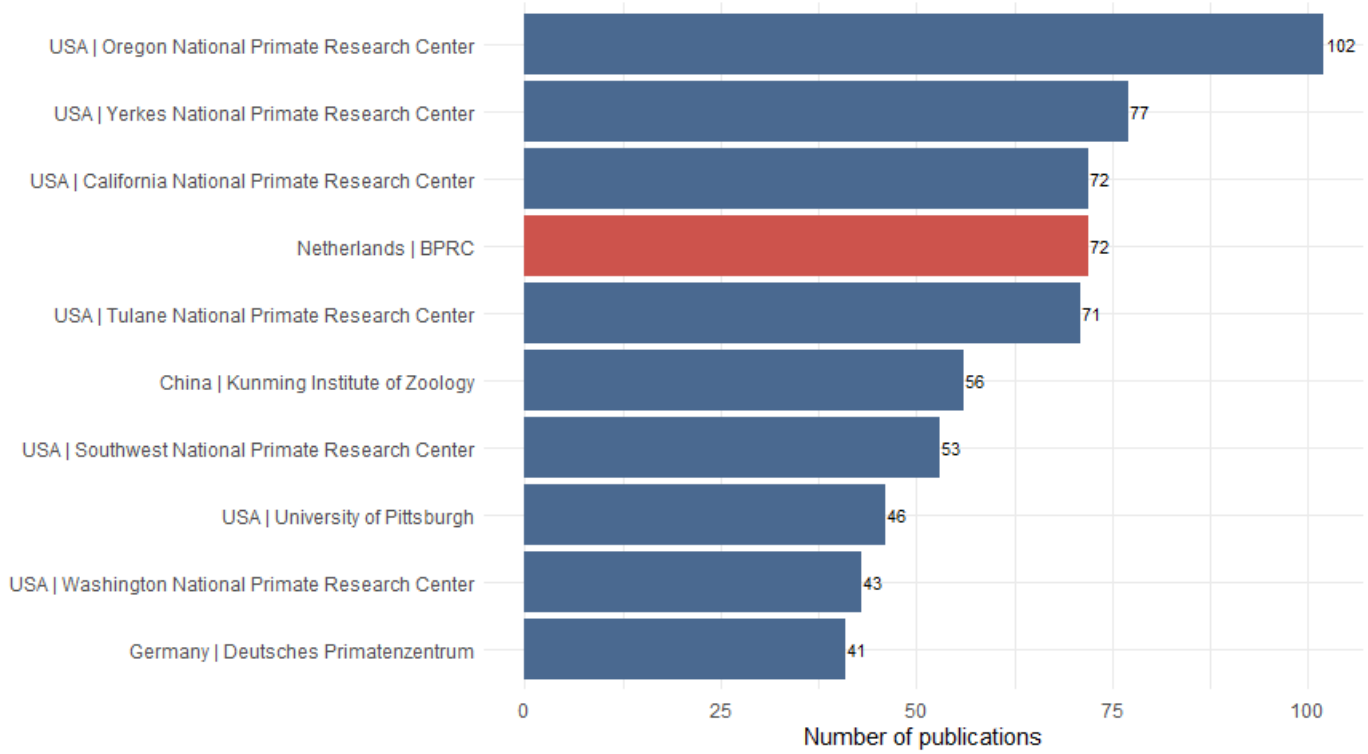


Where is NHP research carried out?

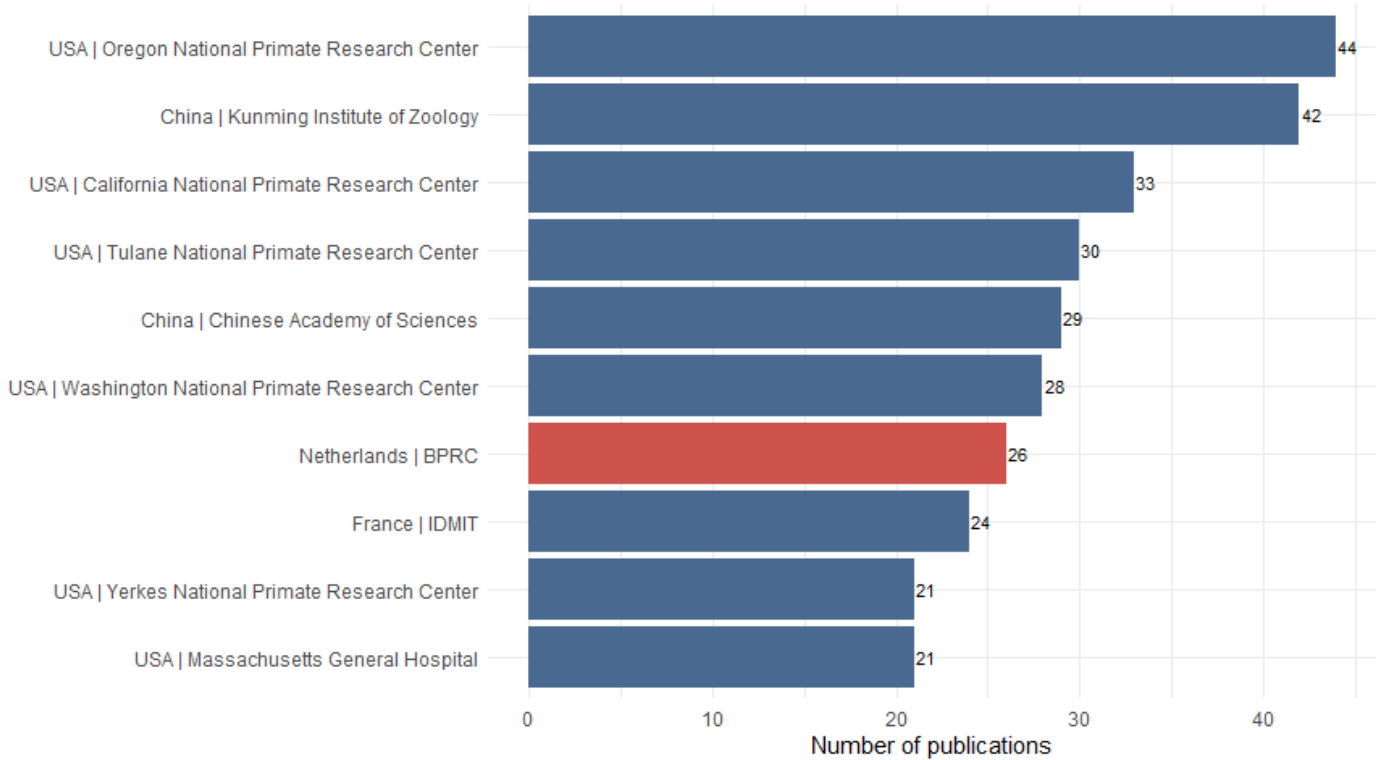
The most productive NHP research centres, in terms of publication numbers, are in the USA. The Netherlands' principle NHP research centre, the BPRC, is the most productive centre in the EU, followed by the German NHP research centre. France is the most productive EU country, but French NHP research is divided across multiple centres.

Filters: primate_used == yes & is_review == "FALSE" & primate_harm_grade != "no harm" & primate_harm_grade != "unknown" & prc != unknown

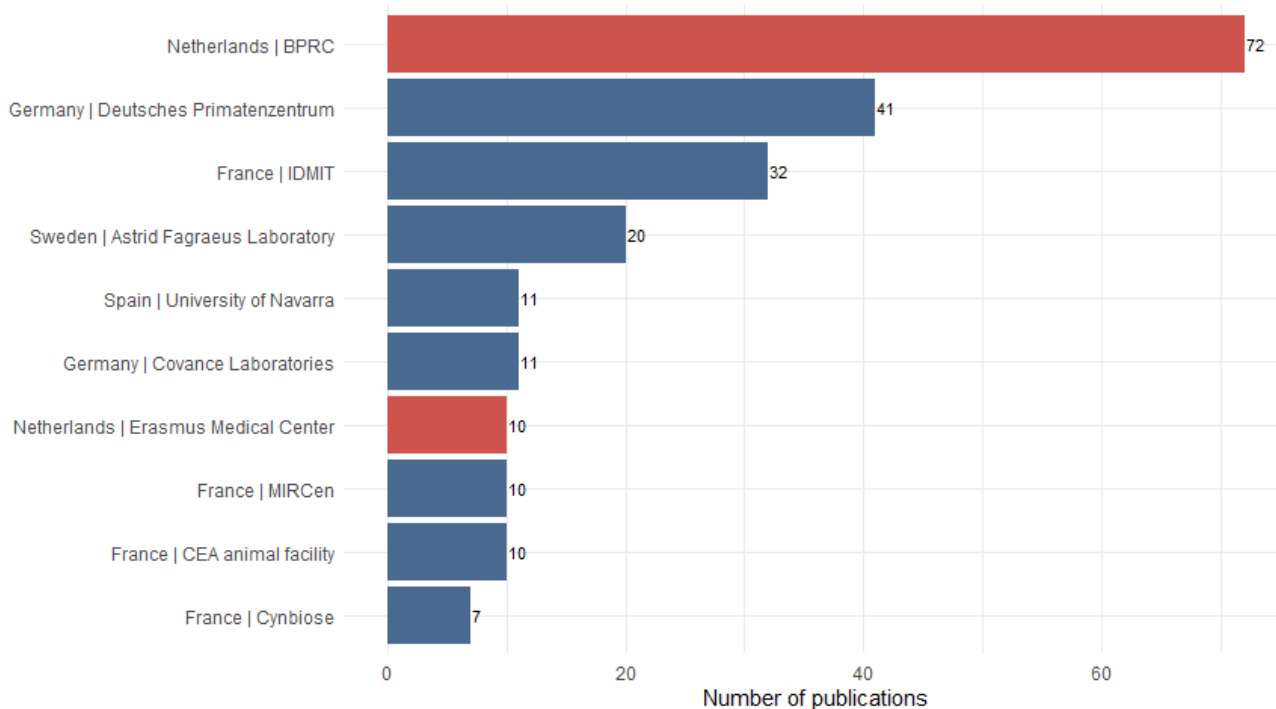
worldwide, since 1986, n = 5195



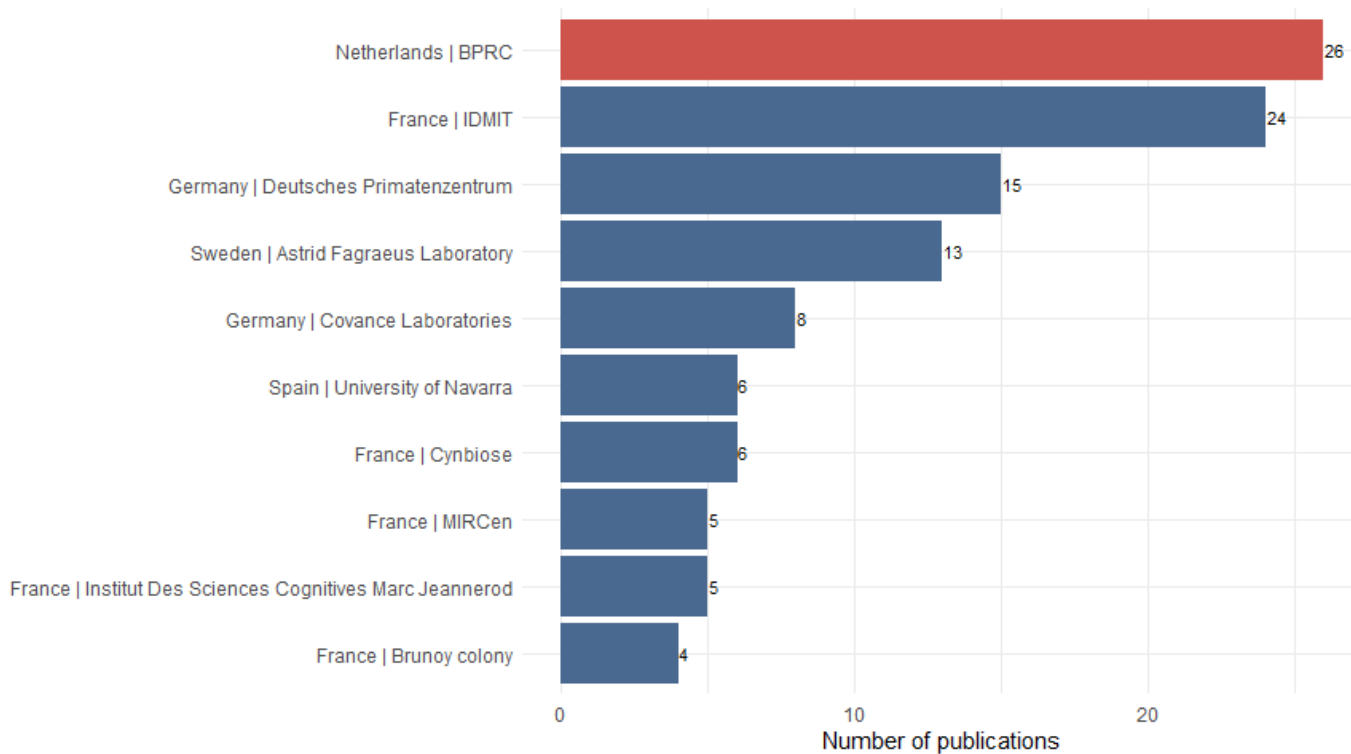
worldwide, since 2019, n = 1974



EU, since 1991, n = 637



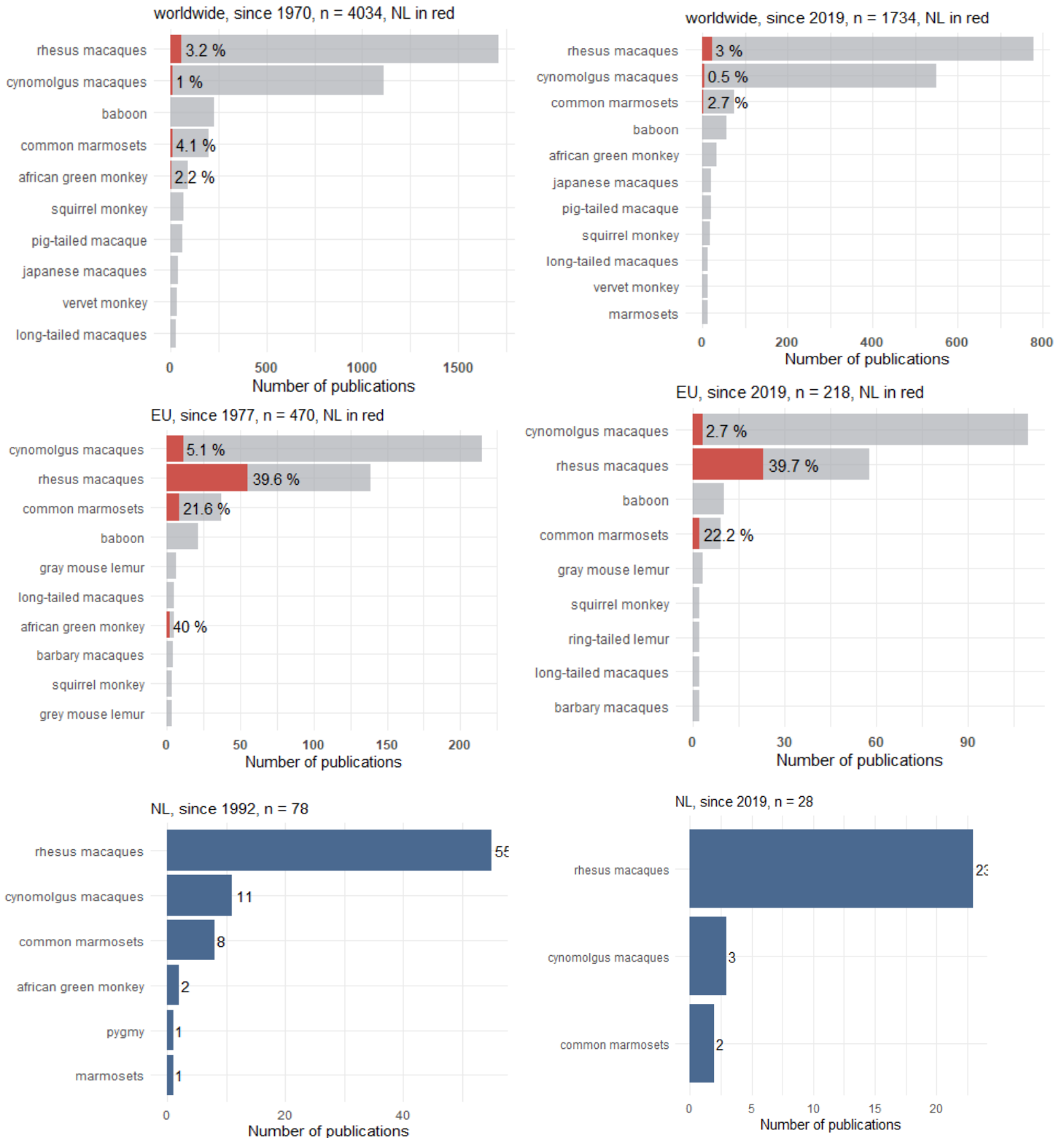
EU, since 2019, n = 232



What animal species are involved?

Rhesus monkeys and long-tailed macaques are the NHPs most commonly used for research. Other species are used as well, but in smaller numbers. The Netherlands is a significant player, accounting for 2.9 per cent of all research with rhesus monkeys worldwide and 33 per cent of research in the EU since 2019.

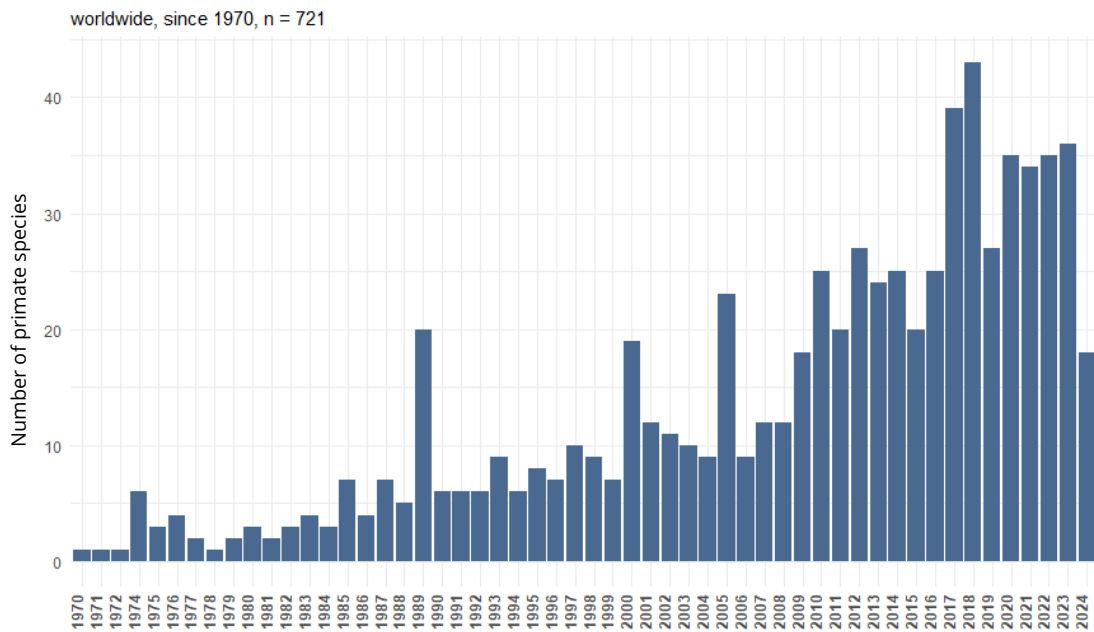
Filters: primate_used == "yes" & is_review == "FALSE" & primate_harm_grade != "no harm" & primate_harm_grade != "unknown" & source == "pdf" & species_common != "" & species_common != "unknown"

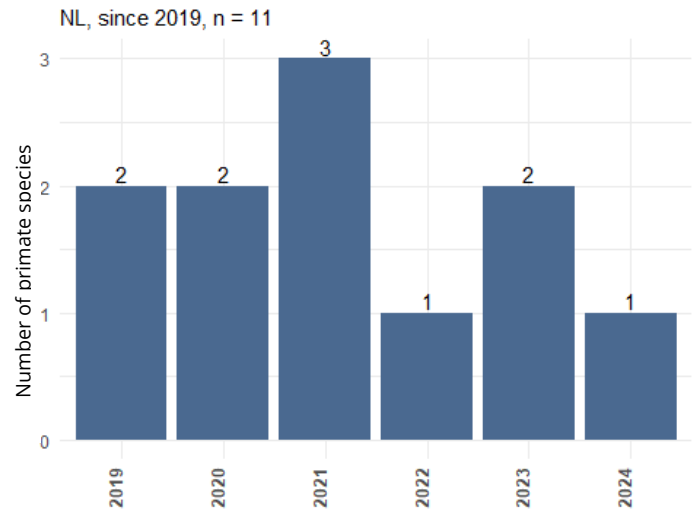
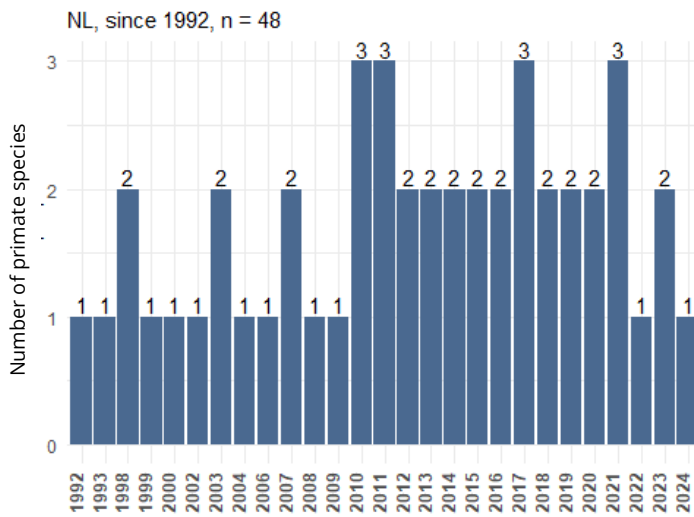
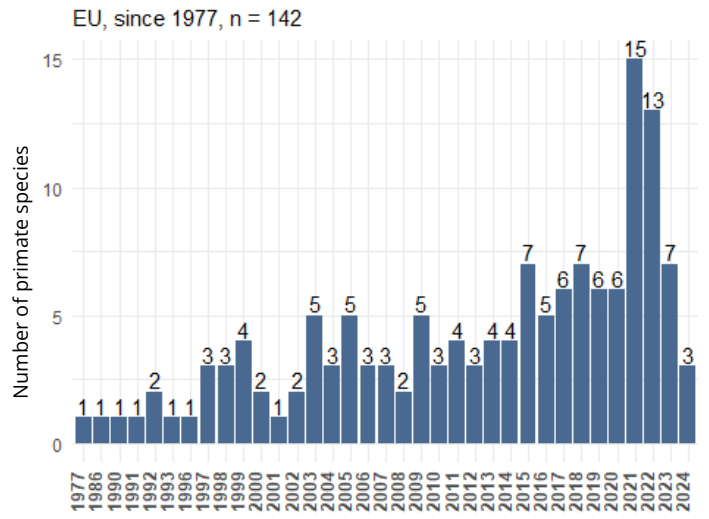
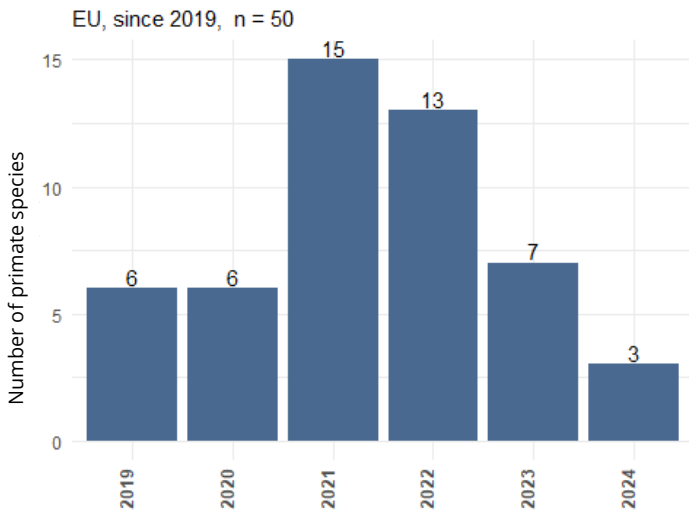


Is the number of NHP species used for research increasing or decreasing?

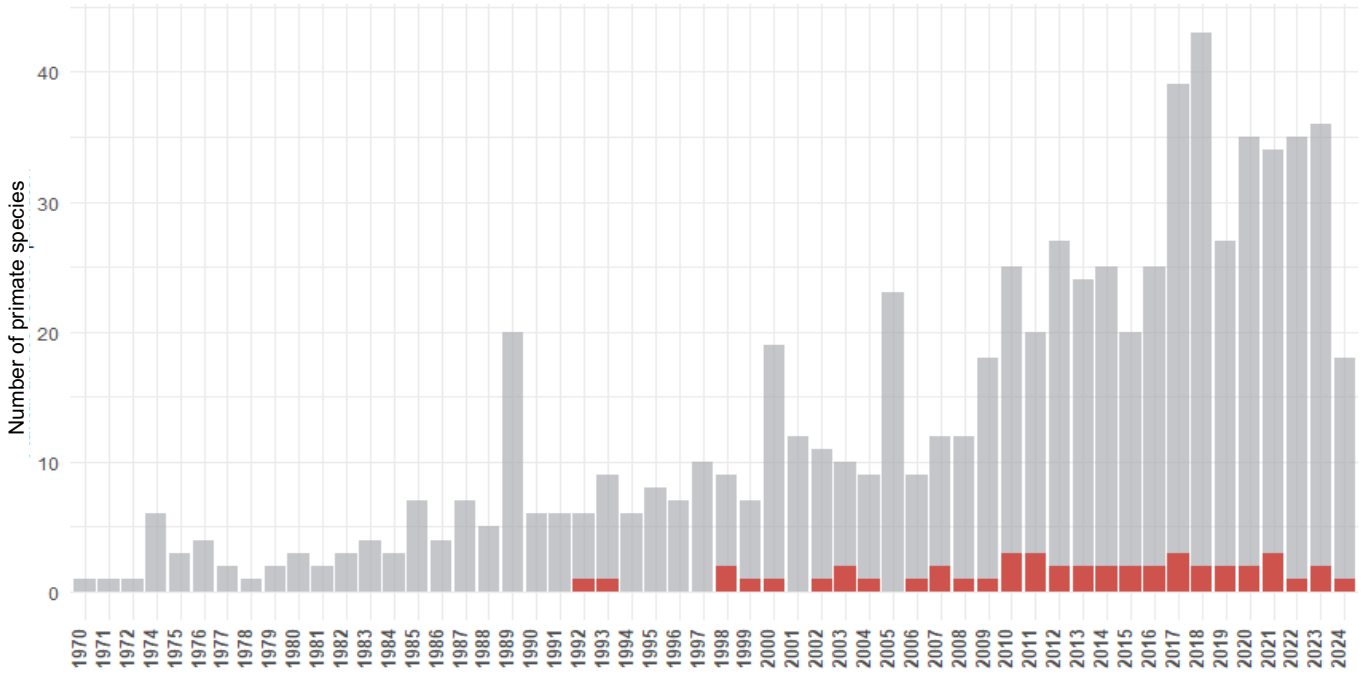
The number of NHP species used for scientific research has increased both globally and within the EU. Analysis of scientific publications indicates that only a small number of NHP species (about two) are used for research in the Netherlands.

Filters: primate_used == "yes" & is_review == "FALSE" & primate_harm_grade != "no harm" & primate_harm_grade != "unknown" & source == "pdf" & species_common != "" & species_common != "unknown"

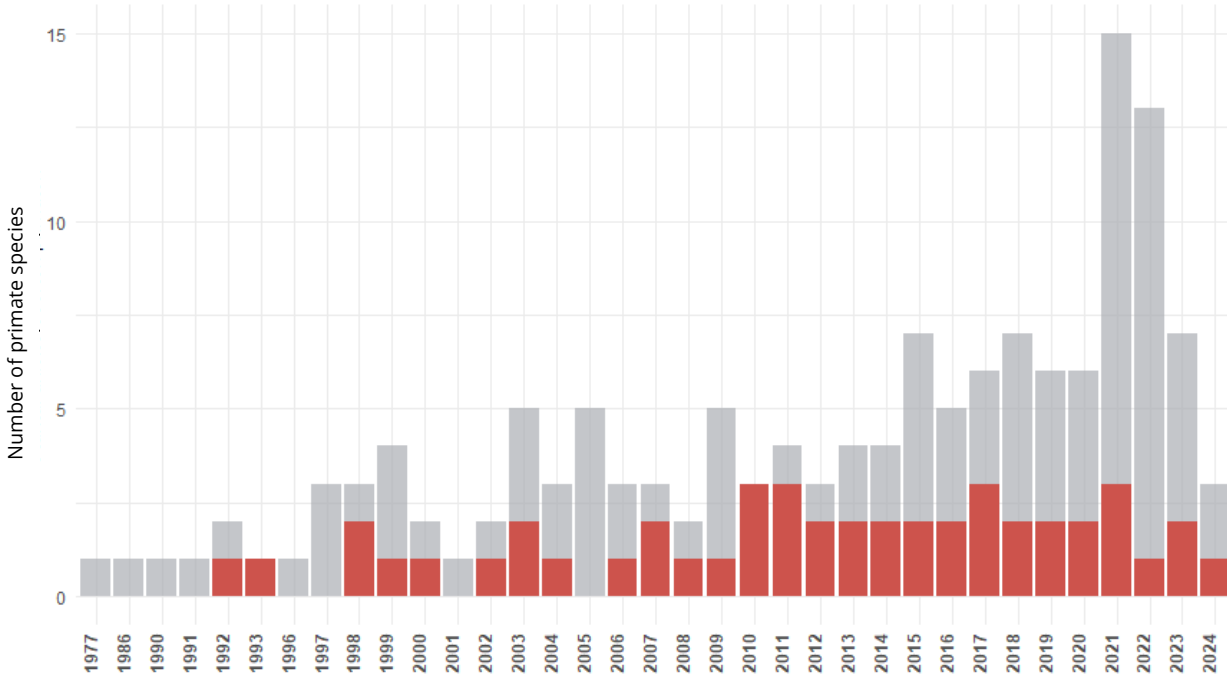




worldwide, since 1970, NL in red, n = 721



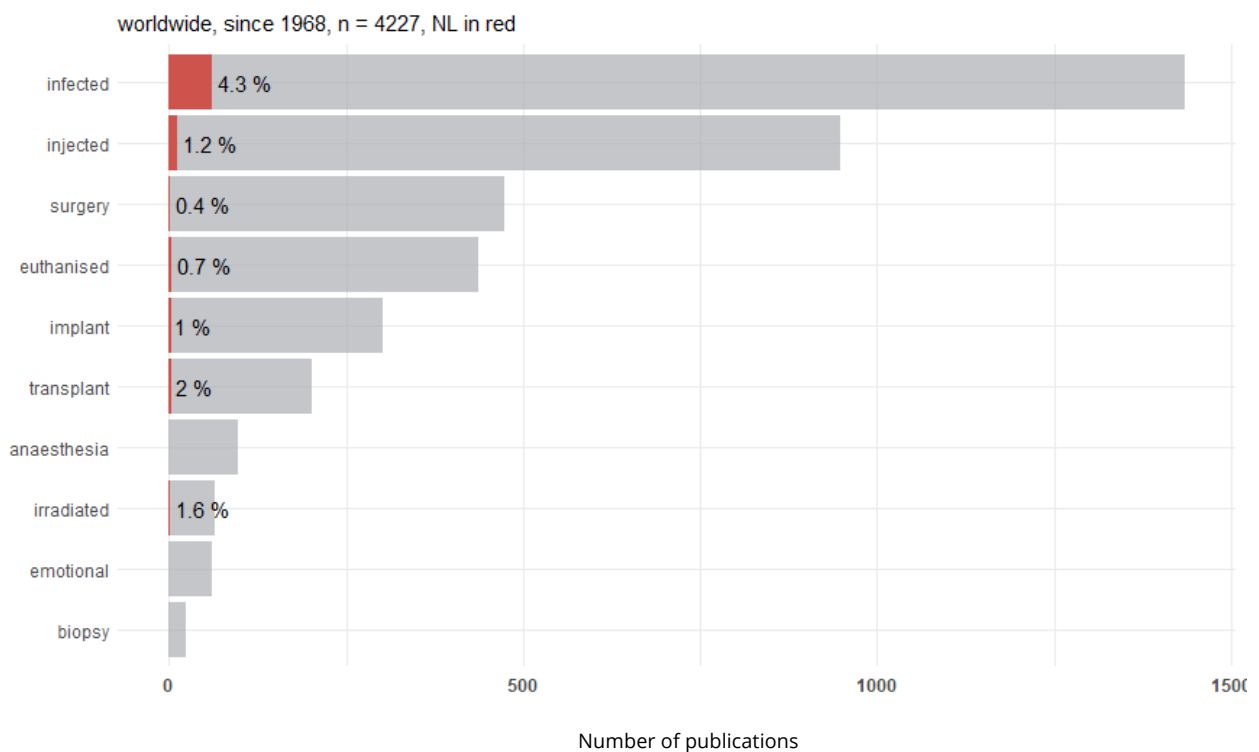
EU since 1977, NL in red, n = 142



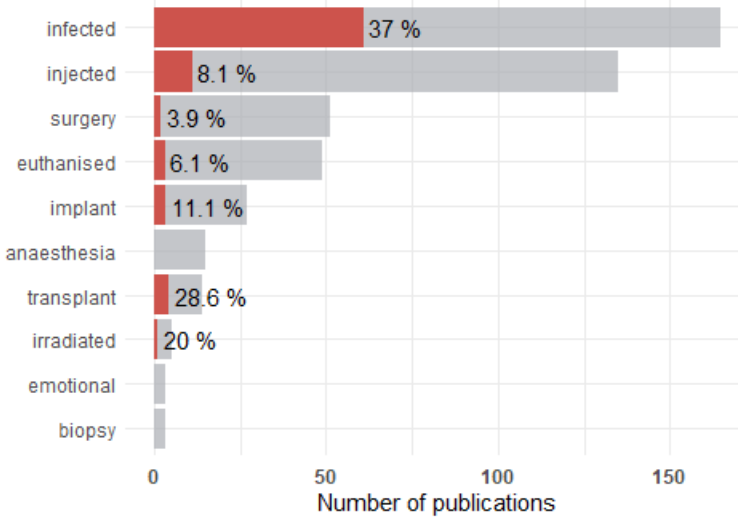
What forms and grades of discomfort do the NHPs experience?

Most of the analysed articles report no discomfort to the NHPs. The studies in question probably involve non-invasive behavioural, cognitive or neurological research, in which NHPs are merely observed. Studies involving no discomfort were excluded from further analysis. Most of the remaining studies, particularly those in the field of infectious disease research, involved mild discomfort. The Netherlands specifically reports a higher frequency of infection experiments involving NHPs – attributable to the emphasis on infectious disease research in the Netherlands.

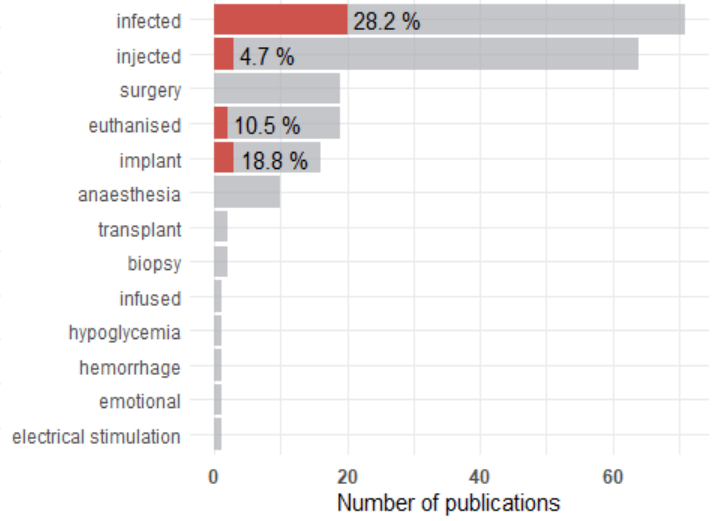
Filter: primate_used == "yes" & is_review == "FALSE" & primate_harm_grade != "no harm" & primate_harm_grade != "unknown" & source == "pdf" & primate_harm != "unknown"



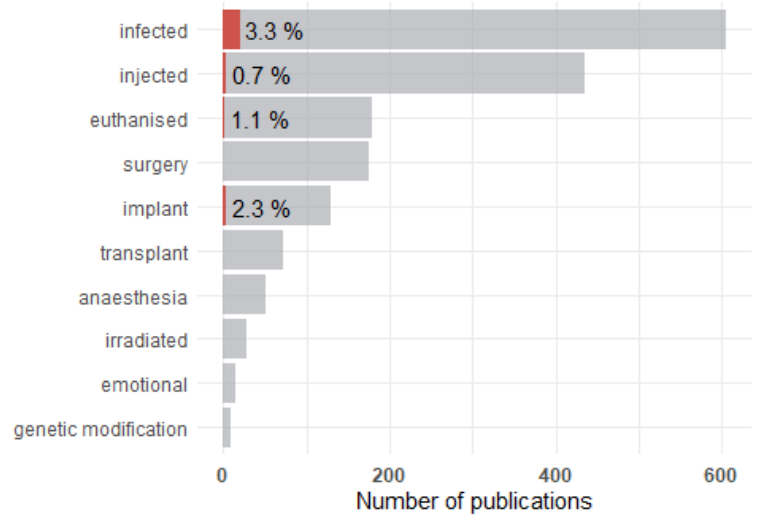
EU, since 1977, n = 479, NL in red



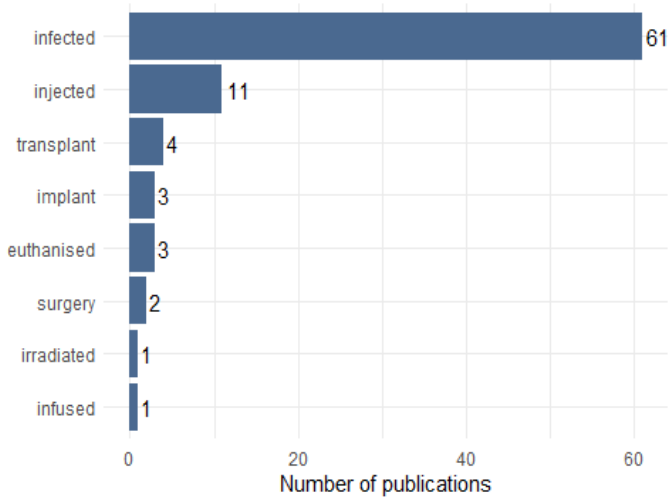
EU, since 2019, n = 208, NL in red



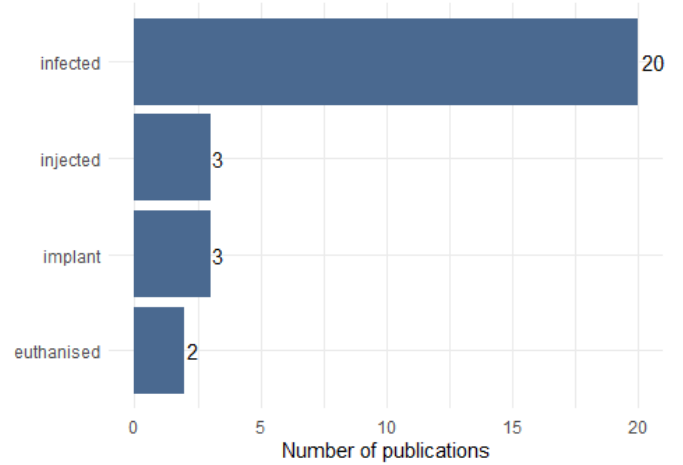
worldwide, since 2019, n = 1773, NL in red



NL, since 1991, n = 86



NL, since 2019, n = 28

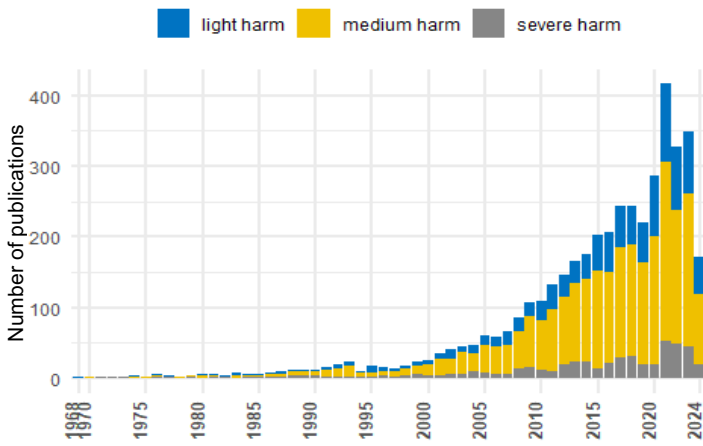


Grade of discomfort by year

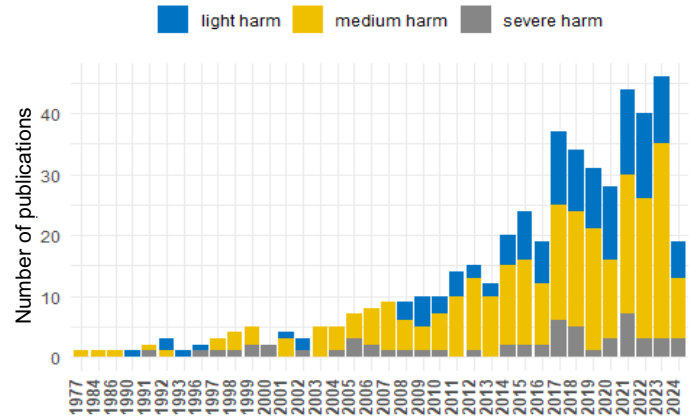
Most publications report a moderate level of discomfort – as associated with infections, injections and general treatments that adversely affect the NHPs' welfare, but from which they are able to recover. Although some studies require the subject animals to be killed, that is uncommon according to the published literature.

Filters: primate_used == "yes" & is_review == "FALSE" & primate_harm_grade != "no harm" & primate_harm_grade != "unknown" & source == "pdf"

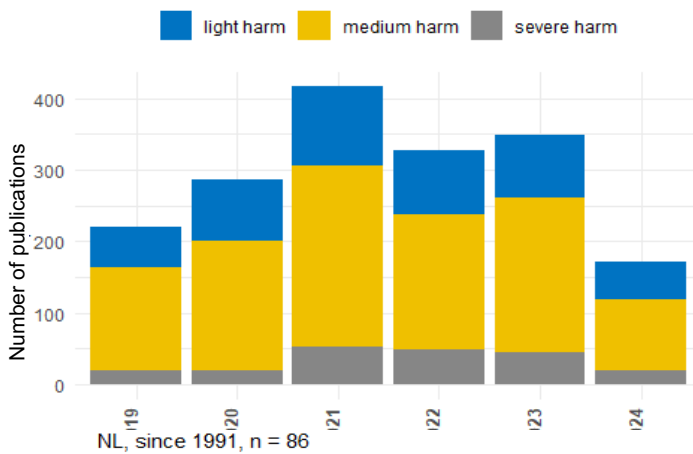
worldwide, since 1968, n = 4224



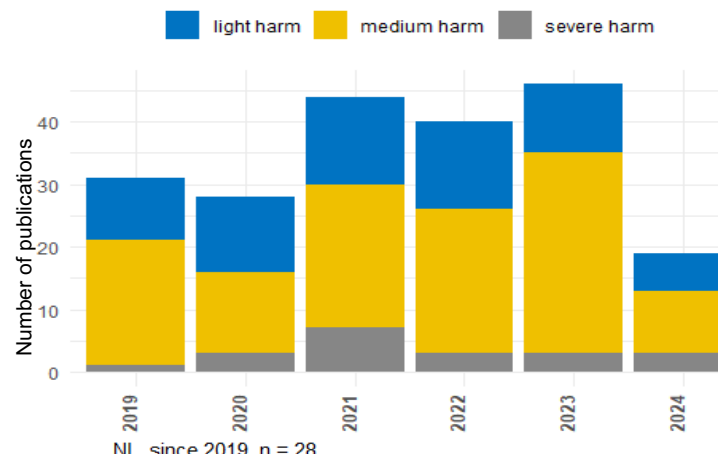
EU, since 1977, n = 479



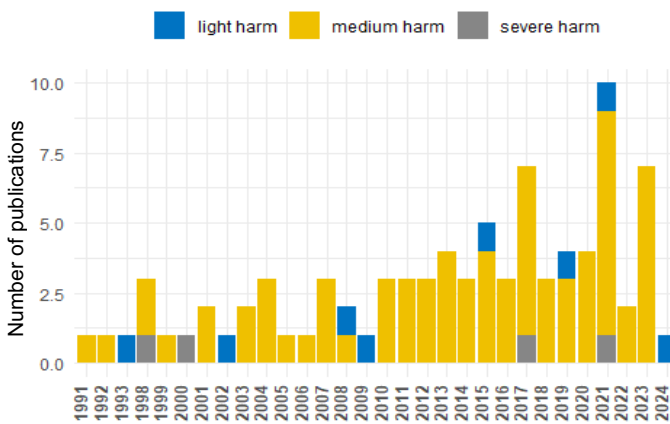
worldwide, since 2019, n = 1771



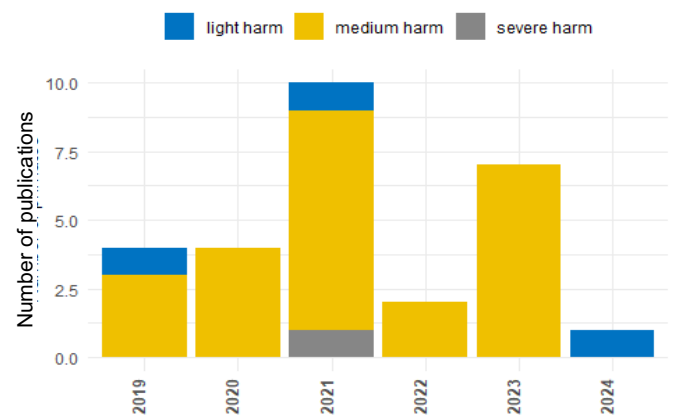
EU, since 2019, n = 208



NL, since 1991, n = 86



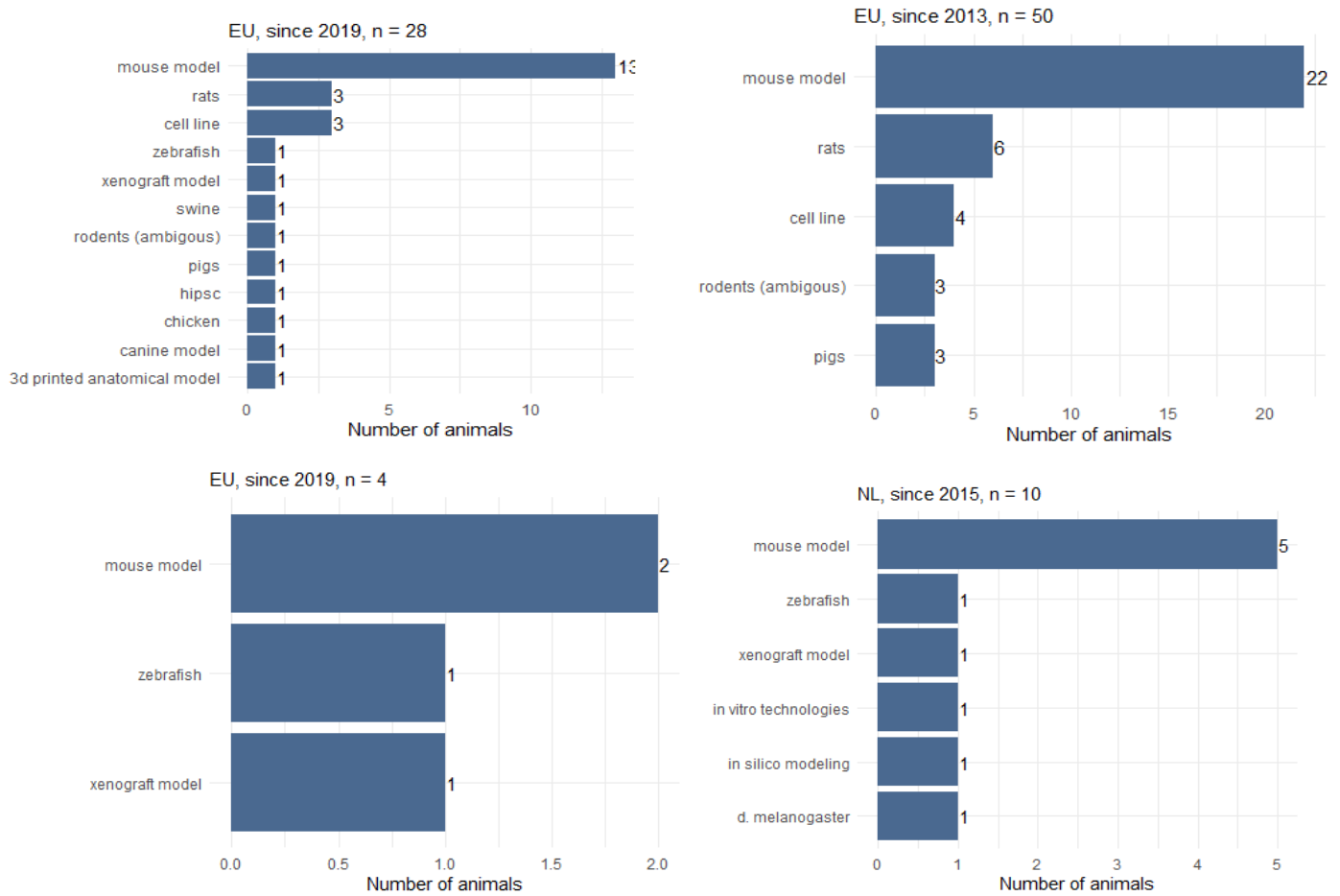
NL, since 2019, n = 28



Has the use of other species of laboratory animals changed as a result of the reduction in the use of NHPs?

Authors are not inclined to suggest alternatives to their models in their manuscripts. Such information can be found more readily in reviews. This question was therefore addressed by selecting studies that referred to NHPs, but were not NHP research reports. In such publications, the laboratory animals most frequently suggested as alternatives to NHPs were rodents. Rodents are widely used as laboratory animals, and they are considerably easier to house than NHPs.

Filters: primate_alt != "unknown" & primate_alt != "No alternatives proposed"



Appendix 2. List of interviewees

The committee was greatly assisted in its work by the opportunity to interview the experts listed below. The experts interviewed by the committee are not responsible for the contents of this report.

1. Bailey, Jarrod: Director of Medical Research, Physicians Committee for Responsible Medicine
2. Bajramovic, Jeffrey: cellular biologist with expertise in in-vitro/animal-free technology, Director of the 3Rs Centre, Utrecht
3. Beken, Sonja: Coordinator, Belgian Federal Agency for Medicines and Health Products (FAMHP)
4. Bontrop, Ronald: Director of the BPRC and Head of the Department of Comparative Genetics & Refinement (now retired); Emeritus Professor of Comparative Immunogenetics of Primates, Utrecht University
5. Bovenkerk, Bernice: Associate Professor of Animal Ethics, Wageningen University
6. Dogterom, Marileen: President of the Royal Netherlands Academy of Arts and Sciences; Professor of Bionanoscience, TU Delft
7. Fentener van Vlissingen, Martje: former Head of Erasmus Animal Experimental Centre, Erasmus MC
8. Fouchier, Ron: Professor of Molecular Virologies and Viroscience, Deputy Head of the Department of Viroscience, Erasmus MC
9. Geijtenbeek, Theo: Professor of Immunology and Infectious Diseases, Amsterdam UMC
10. Gibbs, Sue: Professor of Skin and Mucosa Regenerative Medicine, Amsterdam UMC and ACTA
11. Guernina, Zakia: ad interim General Director, Royal Netherlands Academy of Arts and Sciences
12. Ham, Marieke van: Professor of Biological Immunology, University of Amsterdam, Sanquin Blood Supply and ImmuneHealth XL
13. Hellebrekers, Ludo: Chairman, Central Committee on Animal Experiments
14. Hogervorst, Janneke: Science Advisor, PETA UK
15. Koopmans, Marion: Professor of Virology and Head of the Department of Viroscience, Erasmus MC
16. Langermans, Jan: Head of the BPRC Animal Science Department (ASD) and Deputy Director of the BPRC; Professor of Veterinary Medicine, Utrecht University
17. Meer, van Peter: Senior Assessor at the Medicines Evaluation Board (CBG)
18. Middeldorp, Jinte: Head of the BPRC Department of Neurobiology & Aging
19. Nolte, Martijn: Manager of the More Knowledge with Fewer Animals Programme, ZonMw
20. Prins, Jan-Bas: former member of the National Advisory Committee on Animal Research Policy (NCad); Emeritus Professor of Laboratory Animal Science, Leiden University
21. Manager of the Personalised Health Programme, Hollandbio
22. Project Manager, Hollandbio
23. Rijn, Nicole van: Head of the BPRC Finance Department
24. Ritskes-Hoitinga, Merel: Professor of Evidence-Based Transition to Animal-free Innovations, Utrecht University
25. Roelfsema, Pieter: Professor of Cognitive Neuroscience of Brain Stimulation, Netherlands Institute for Neuroscience (NIN), KNAW
26. Roestenberg, Meta: Professor of Human Models for Vaccine Development, Leiden University Medical Centre

27. Salvatori, Daniela: Professor of Comparative Anatomy and Physiology, Head of the Department of Anatomy and Physiology, Chair of Utrecht TPI Programme, Utrecht University, interim Scientific Director CABT
28. Schuurman, Rick: Professor of Neurodegeneration, Systems & Network Neuroscience, Amsterdam UMC
29. Smid, Henk: Chairman of the National Advisory Committee on Animal Research Policy (NCad)
30. Teunis, Marc: Associate Lector, Data Science in Life Sciences & Chemistry, Utrecht University of Applied Sciences
31. Vermeire, Theo: Toxicologist, RIVM (now retired)
32. Via, Laura: Associate Staff Scientist, National Institute of Allergy and Infectious Diseases (NIAID)
33. Weijers, Debby: Director of the Dutch Society for the Replacement of Animal Testing (*Stichting Proefdiervrij*)
34. Wezel, Richard van: Professor of Visual Neuroscience, Radboud University; Director of Health at OnePlanet Research Center, Donders Centre for Neuroscience
35. Wolthers, Katja: Senior Clinical Virologist, MD PhD, consultant and PI in Molecular Epidemiology and Pathogenesis of Human Picornaviruses, Amsterdam UMC
36. Zeeuw, Chris de: Professor of Neurosciences and Head of the Department of Neuroscience, Erasmus MC & principal investigator, Netherlands Institute for Neuroscience (NIN), KNAW
37. Zeldenrust, Fleur: Associate Professor at the Donders Institute for Brain, Cognition and Behaviour, Radboud University

Appendix 3: Participants in consultations

The committee was greatly assisted in its work by the opportunity to hold two consultation meetings with the experts listed below. The experts consulted by the committee are not responsible for the contents of this report.

Participants in consultation meeting with NAM researchers

1. Beekman, Jeffrey, Professor of Cellular Disease Models, UMC Utrecht
2. Gibbs, Sue: Professor of Skin and Mucosa Regenerative Medicine, Amsterdam UMC
3. Heine, Vivi: Professor of Human Model Systems, Amsterdam UMC & Vrije Universiteit Amsterdam
4. Lammertse, Hanna: Project Leader hiPSC & Organ-on-Chip Centre, Leiden UMC & Manager Infrastructure, Institute for human Organ and Disease Model Technologies (hDMT)
5. Ritskes-Hoitinga, Merel: Professor of Evidence-Based Transition to Animal-free Innovations, Utrecht University
6. Teunis, Marc: Associate Lector, Data Science in Life Sciences & Chemistry, Utrecht University of Applied Sciences

Participants in consultation meeting with civil society representatives

1. Bertens, Peter: Innovative Medicines Association
2. Boon, Luuk-Jan: former Director of the Eye Association Netherlands (*Oogvereniging*)
3. Burgers, Anne: Science and Innovation Advisor, Dutch Society for the Replacement of Animal Testing (*Stichting Proefdiervrij*)
4. Hogervorst, Janneke: PETA UK
5. Nolte, Martijn: in a personal capacity, contributing experience gained at ZonMw
6. Saaltink, Dirk-Jan: Senior Knowledge & Innovation Officer, Dutch Brain Foundation
7. Smit, Cees: VSOP – Patients' umbrella organisation for rare and genetic disorders

Appendix 4. Historical context

Animal research, including that on non-human primates (NHP), was not regulated until the introduction of the Animal Experiments Act (WoD) in 1977. However, animal research had a long history prior to the WoD, and had been the subject of debate, as animal ethics developed within society and in legislation. That process started in 1881, when the Dutch parliament first debated whether animal cruelty should be criminalised. This led to the following provision being added to the Dutch Penal Code:

'He who intentionally and unlawfully destroys, damages, renders unusable or removes any property belonging wholly or partly to another shall be punished with imprisonment for a term not exceeding two years or a fine not exceeding three hundred guilders. Equal punishment shall be applied to him who intentionally and unlawfully kills, damages, disables or disposes of an animal belonging wholly or partly to another.'²⁵⁴

To prevent acceptable activities being criminalised by the new provisions, it was decided that only 'deliberately cruel' treatment of animals would be punishable.²⁵⁵ The intention of the legislative was to avoid criminalising legitimate activities, in the context of which suffering was inflicted on animals. The main activities that the legislative wanted to protect were veterinary procedures, but the use of laboratory animals was also covered. Notably, the new provisions were not concerned with the intrinsic value of an animal, merely with the infliction of suffering on an animal owned by another person.²⁵⁶ Laboratory animals were excluded from the animal cruelty prohibition because, according to the legislative, such animals could be entrusted to the care of researchers.²⁵⁷

From the parliamentary debate regarding the cruelty prohibition in 1880, it is apparent that the government was indeed asked to regulate the practice of vivisection. In 1883, the then Minister of the Interior asked the KNAW to investigate vivisection practices at universities. The conclusion was that there was no evidence of abuse. In 1885, the Minister asked the medical faculties whether they thought vivisection should be regulated in the Netherlands, as it was in Germany. The faculties generally felt that regulation was unnecessary and could hamper scientific research.²⁵⁸

In 1907, a state commission was set up for the first time to consider whether the legal regulation of animal research was desirable. That led to a comprehensive report, which recommended a licensing system with legal requirements to assure the proper treatment of laboratory animals. However, no regulations were ultimately introduced. The investigation prompted strong criticism from the medical community at the time. The report was interpreted as critical of the way that animal research was being conducted at the time, and the medical community felt compelled to point out how valuable animal research was to science. It was also felt that, in countries where legal

²⁵⁴ Dutch Penal Code, Article 254.

²⁵⁵ Michiels van Verduijnen, *Eenige opmerkingen over dieren mishandeling naar aanleiding van de artikelen 254, 350 en 455 van het nieuwe wetboek van strafrecht* [Observations regarding animal abuse, pertaining to Articles 254, 350 and 455 of the new Penal Code].

²⁵⁶ Smidt, *Geschiedenis van het wetboek van strafrecht: volledige verzameling van regeeringsontwerpen, gewisselde stukken, gevoerde beraadslagen, enz* [History of the Penal Code: a comprehensive collection of government proposals, substituted items, debates, etc].

²⁵⁷ Bordes, 'Dieren in het geding Een juridisch-historische analyse van het verbod op dieren mishandeling' [Legal debate regarding animals: a legal-historical analysis of the prohibition of animal abuse].

²⁵⁸ Freriks et al., 'Noodzakelijk kwaad: Evaluatie van de Wet op dierproeven' [Necessary evil: An evaluation of the Animal Experiments Act].

restrictions had been placed on vivisection, scientific research had suffered as a consequence.²⁵⁹ The researchers who evaluated the Wod in 2005 noted that attempts to legally regulate animal research had always encountered the argument that new regulations would hamper scientific progress, and still did.

In 1920, the Penal Code's prohibition of animal cruelty was revised, and a new penalty and offence definition were introduced:

'Punishable with imprisonment of not more than six months or a fine of not more than three hundred guilders: 1°. any person who, without reasonable cause or beyond what is permissible to achieve such cause, intentionally causes pain or injury to an animal or harms the health of an animal'

The 'intentionality' criterion of the old provision had proven difficult to meet in practice. A 'reasonable purpose' criterion was added to the new provision, which now forced the court to weigh up the interests at stake. The change should in theory have criminalised more activities. Although laboratory animals were still excluded from the new provisions, the change to the law made in 1920 does illustrate how the ethics of human behaviour towards animals were developing.

In 1933, there was renewed debate about the possible regulation of animal research. The Minister of the Interior wrote about complaints about vivisection practices, in response to which the Health Council had set up a committee to re-examine the issue. The committee also took the view that regulation was desirable, and recommended a licensing system for animal research. However, no new legislation was forthcoming. It is also worth noting that, in 1954, a Health Council advisory committee subsequently produced a report on the matter, which reached very different conclusions. The later committee saw no grounds for regulating animal research and advised against it, on the grounds that the implications for science would be too great. However, the State Secretary for Social Affairs and Health nevertheless took the view that a licensing system with registration and inspection requirements should be considered. That would require further investigation.

In 1955, a bill proposing a new Animal Protection Act was presented to parliament. The bill featured provisions for the introduction of statutory regulations on the use of laboratory animals. Other provisions included the creation of a Council for the Protection of Animals and the prohibition of battery coops in poultry farming. However, in the six years it took for the bill to pass through parliament, many of its original provisions were removed. So, for example, no Animal Protection Council was created, and battery coops were not outlawed. The use of laboratory animals was barely even discussed, because the government claimed not to have the information it required to do so.²⁶⁰ The government considered that it would be useful to first investigate the experiences of countries that already had such regulations (the UK and Germany). In 1961, that commitment was repeated, leading to the establishment of an interdepartmental working group to investigate animal research in the Netherlands. After publishing a national survey in 1964, the working group published a report in 1966. The working group's report emphasised the need for animal research, but considered regulation necessary to promote efficient use of and proper care for laboratory animals, and to prevent excesses. It also recommended the introduction of a licensing system,

²⁵⁹ State Secretary for Social Affairs and Health, *Memorie van toelichting – Wijziging van de Wet op de dierproeven* [Explanatory Memorandum – Amendment to the Animal Experiments Act].

²⁶⁰ Bordes, *Dieren in het geding Een juridisch-historische analyse van het verbod op dierenmishandeling* [Legal debate regarding animals: a legal-historical analysis of the prohibition of animal abuse].

overseen by an inspectorate. The report ultimately formed the basis for the Animal Experiments Bill, which was presented to the House of Representatives in 1970.²⁶¹

Animal Experiments Act and the first Animal Experiments Directive (1977-2010)

The first Animal Experiments Act came into force in 1977, creating a legal framework for conducting animal research. For the first time, animal research was subject to rules and regulations intended to assure animal welfare. The law required researchers to obtain licences before carrying out animal research. A licence would only be given if certain conditions were met, such as minimising the number of animals used and minimising the suffering experienced by the animals. Inspections were to be performed to make sure that the conditions were met. The law also emphasised certain ethical considerations concerning animal research. Researchers were encouraged to consider alternative methods and to assure animal welfare as far as possible.

In 1986, the European Directive 86/609/EEC was adopted to eliminate disparities between member states regarding the protection of animals used for experimental and other scientific purposes. That led to the Wod being revised, for example to require that advice be sought from a DEC before conducting animal research, and to tighten up the licensing system. DEC's have the task of reviewing the ethical aspects of animal research proposals, and providing advice on the suitability and ethical acceptability of the proposed research methods.

The 2005 evaluation of the Wod endorsed the importance of ethical review by DEC's, but also stated that the system was far from perfect. For instance, decision-making regarding licences was not covered by the General Administrative Law Act and the enforcement structure was inadequate. The evaluation group also concluded that the intrinsic value of an animal was not an independent consideration in the context of an ethical review. When reviewing a research proposal, a DEC considers only reduction, refinement and replacement (the three Rs).²⁶²

The Wod was amended several times prior to the system change in 2014. A key change was made to the Wod in 1997. Since then, it has in principle been against the law in the Netherlands to test cosmetics on animals. The use of wild animals or pets for laboratory research is now also prohibited. In the autumn of 2003, the Wod was amended again to prohibit experiments on great apes. The Netherlands was the last country in the EU where such experiments were still performed. In the rest of the EU, no research had been conducted on great apes since 1999. However, research with great apes was not formally prohibited throughout the EU until 2010, when EU Directive 2010/63/EU came into effect.

New Animal Experiments Directive and system change (2010-2014)

In 2010, European Directive 2010/63/EU came into force. The directive was intended to ensure a level of protection for laboratory animals, based on application of the three Rs, throughout the EU. A further intention was to largely eliminate differences between EU member states in terms of the laws and regulations that apply to laboratory animals and animal research (*level playing field*). However, EU directives are not themselves laws; they have to be translated into national legislation by member states. Furthermore, member states have the freedom to interpret some aspects of the directive as they see fit, and, in certain areas, to follow a policy that is stricter than that required by

²⁶¹ State Secretary for Social Affairs and Health, *Memorie van toelichting – Wijziging van de Wet op de dierproeven* [Explanatory Memorandum – Amendment to the Animal Experiments Act].

²⁶² The evaluation was overseen by ZonMw; for summary conclusions, see also: State Secretary for Social Affairs and Health, *Memorie van toelichting – Wijziging van de Wet op de dierproeven* [Explanatory Memorandum – Amendment to the Animal Experiments Act].

the directive. Consequently, there are still differences in the way animal research is regulated within the EU.

The directive was implemented in Dutch law in 2014, by means of the Animal Experiments Act. The Act significantly changed the licensing system. Instead of being able to seek a licence from any DEC, researchers had to apply to a newly established central licensing authority, the CCD. The DECs took on a 'merely' advisory role. The National Advisory Committee on Animal Research Policy (NCad) was also established by the revised Wod. The NCad is an independent advisory body tasked with advising the government and the CCD.

The scope of the legislation was also made wider than it had been under the old Animal Experiments Directive. In addition to vertebrates, the revised Act applied to cephalopods (octopuses and squids). There is scientific evidence that cephalopods can experience pain, suffering, anxiety and permanent (mental) harm. The Directive also introduced the current strict rules on the use of non-human primates in animal research.

Dutch ambitions regarding animal-free alternatives (2014-present)

Since the Wod was amended in 2014 to bring it into line with the new Animal Experiments Directive, the Netherlands has expressed great ambitions regarding the phase-out of animal research. In 2016, then State Secretary Van Dam said that the government had the ambition to make the Netherlands a leader in animal-free innovation by 2025. In line with that ambition, the NCad brought out its advisory report 'Transition to Animal-Free Research'.²⁶³

Since 2017, the Animal-Free Innovation Transition Programme (TPI Programme) has been in place to support Dutch policy ambitions. The TPI Programme operates under the banner of the Ministry of LNV, and various stakeholder organisations (including ministries and knowledge centres) collaborate in the programme on projects to promote animal-free innovation. The programme focuses on several aspects, including research into and development of alternative methods, knowledge sharing and collaboration. The NCad and the TPI Programme have also promoted the development of so-called 'roadmaps'. A roadmap is a document in which a scientific field sets out its ambition to bring about animal-free innovation.

In the House of Representatives, animal research and animal-free innovation have continued to receive considerable attention. In 2017, the Rathenau Institute also undertook an exploratory study, resulting in the report '*Van Aap naar Beter*' ('From Primate to Wellness').²⁶⁴ The study was prompted by the House of Representatives' desire for the number of experiments on non-human primates carried out in the Netherlands to be reduced, ultimately to zero, as soon as possible. A motion was also passed in 2019, calling for acceleration of the transition to animal-free innovation.

In 2020, the coronavirus pandemic hit the Netherlands and the rest of the world. Research on NHPs played an important role in the development of vaccines, further highlighting the scientific importance of research on laboratory animals in general and NHPs in particular. Nevertheless, the Dutch government has continued to emphasise the importance of the transition to animal-free

²⁶³ NCad, 'Transitie naar proefdiervrij onderzoek – Over mogelijkheden voor het uitfaseren van dierproeven en het stimuleren van proefdiervrije innovatie' ['Transition to animal-free research – About the scope for phasing out animal research and promoting animal-free innovation'].

²⁶⁴ Rathenau Instituut, '*Van Aap naar beter. Een verkenning en dialoog over proeven met apen*' ['From Primate to Wellness. An exploration and dialogue regarding experimentation on primates']

alternatives, partly in response to the House motion referred to above. In 2020, it was decided that the TPI Programme should be extended and intensified.²⁶⁵

²⁶⁵ Parliamentary Papers, 2019, 32336-102 Motion by Member De Groot on promoting the transition to animal-free innovation

Appendix 5: The Committee's assignment

The assignment given to the NHP Research Committee derives from the motion proposed to the House of Representatives by Member Wassenberg and passed unanimously on 24 November 2022.²⁶⁶ On 6 July 2023, the Minister of OCW wrote to parliament explaining how he intended to implement that motion.²⁶⁷ On 5 December 2023, the minister signed the order establishing the committee, which was published in the Government Gazette on 5 February 2024.²⁶⁸

Motion by Member Wassenberg et al, 24 November 2022

The House,

having heard the deliberations,

noting that the Chamber wishes to entirely phase out experiments on non-human primates as soon as possible and as soon as it is safe to do so (unanimously adopted motion 32 336, no. 57 by members Van Dekken and Heerema); noting that the Minister of OCW called the 40% reduction in animal experiments on primates the first step in the implementation of that motion (32 336, no. 72);

noting that the reduction must be achieved by 2025;

requests the government to commission an inquiry during 2023 into the possibility of further reducing the number of experiments on non-human primates without affecting the research strictly necessary to control life-threatening diseases and outbreaks of infectious diseases that threaten public health, in line with the wish of the House (as expressed in motion 32 336, no. 57);

calls on the government to arrange for such an inquiry to be conducted by independent experts,

and moves on to the order of the day.

Wassenberg
Van der Woude
De Hoop
Beertema
Kwint
Sylvana Simons
Dassen
Van Baarle
Van der Plas
Omtzigt
Westerveld
Van der Molen

²⁶⁶ House of Representatives, *Motie van het lid Wassenberg c.s. over een onderzoek naar de mogelijkheid om het aantal proeven op niet-humane primaten verder te verlagen* [House of Representatives, Motion by Member Wassenberg et al. regarding research into the possibility of further reducing experiments on non-human primates].

²⁶⁷ Minister of OCW, *Voortgang onderzoek verdere verlaging proeven op niet-humane primaten (motie Wassenberg c.s.)* [Progress of research into the further reduction of experiments on non-human primates (motion by Wassenberg et al.)].

²⁶⁸ Minister of OCW, *Instellingsbesluit Commissie onderzoek niet-humane primaten* [Order Establishing the Committee on Research Involving Non-Human Primates].

Bisschop
Segers
Van der Laan
Pouw-Verweij
Gündoğan
Den Haan
Dekker
Van Haga

Letter to parliament, 6 July 2023

To the Speaker of the House of Representatives of the Netherlands
P.O. Box 20018
2500 EA THE HAGUE

**Science and Research
Policy**
Rijnstraat 50
The Hague
PO Box 16375
2500 BJ The Hague
www.rijksoverheid.nl

Date 6 July 2023
Subject Progress of research into the further reduction of experiments on non-human primates (motion by Wassenberg et al.)

Our reference
38591292

During the budget debate regarding the Ministry of Education, Culture and Science (OCW) on 24 November last, the motion of member Wassenberg et al²⁶⁹ was adopted unanimously. That motion calls on the government to commission an inquiry in 2023 into the possibility of further reducing the number of experiments on non-human primates. I am accordingly writing to inform the House how I intend to give effect to that motion.

Details of the inquiry

The main question to be addressed by the inquiry is as follows: what scope is there for further reducing the number of experiments on non-human primates, without affecting the research strictly necessary to control life-threatening diseases and outbreaks of infectious diseases that threaten public health. In that context, I wish to know what types of research with non-human primates remain necessary for the purpose of controlling life-threatening diseases and outbreaks of infectious diseases that threaten public health, and under what circumstances such research can be further phased out in the future. I also wish to know whether the remaining research with non-human primates can be phased out entirely, and how that could be done as soon as possible. I am emphatically not asking for policy advice, but for an investigation into what can and cannot be done.

To provide answers to the main question, I wish an inquiry to be undertaken with three elements. First, a shared picture should be obtained that can serve as a starting point for the rest of the inquiry. To that end, definitions, figures and facts – such as the numbers of experiments carried out on non-human primates, the purposes of the research in question, and (international) trends and developments – should be provided. In this first phase of the inquiry, the meaning of the demarcation criterion ‘life-threatening disease’ should be clarified. The reason being that there are diseases that are not life-threatening in a person without comorbidity, but can be life-threatening in (very) vulnerable patients. In addition, there are conditions that, while not life-threatening, can have a profound impact on the well-being of patients and those around them.

²⁶⁹ Parliamentary Paper: 2022D49960.

The second part of the inquiry is to address the potential for further reducing the number of experiments involving non-human primates in the Netherlands. Clarity is required as to whether such a reduction can be achieved safely and quickly, and, if so, how. I wish to see that other ways of performing the research that is currently carried out using non-human primates are investigated. In that context, I wish not only that consideration be given to possible means of replacement, reduction and refinement, but also that the potential for using alternative technologies, such as *organ-on-a-chip* and *organoids*, be explored and taken into account.

In this second phase of the inquiry, it will be important that the feasibility and implications of the various options are considered in the round. Consideration may be given to the effects on science and basic research, on the Netherlands' capacity for innovation, and on the number and welfare of the non-human primates used in the Netherlands, Europe and globally. International developments are relevant to the inquiry. I therefore wish to see consideration given to Europe's strategic autonomy and (the scope for reducing) dependence on other countries in fields such as vaccine development.

I expect the inquiry to yield several scenarios, including the scientific, ethical, legal, economic, international and societal implications of each. As indicated above, the phase-out of research with non-human primates must be considered in an international context. Therefore, the third and final phase of the inquiry is to consist of a review by international experts. The inclusion of such a review will also assure the quality and independence of the inquiry.

Performance and supervision of the inquiry

In order to ensure that the inquiry is performed in a thorough, independent manner, I will establish a balanced committee, made up of experts in various fields. As committee chair, I will appoint someone who can demonstrably act independently and accordingly has no direct allegiance to biomedical research, animal advocacy or animal-free alternatives. In addition to managerial experience, the chair will also have extensive experience in public debate and political decision-making on issues relating to scientific and technological developments.

The committee as a whole must possess demonstrably adequate familiarity with the ethical aspects of science and/or (animal) ethics; the (bio)medical sciences and the use of animal research; alternative technologies; infectious diseases and life-threatening diseases. When appointing the committee, I will also take into account the independence of the experts in relation to research with non-human primates, the involvement of prospective committee members in the transition to animal-free innovation, and the age profile of the committee. The committee will be supported and assisted by a consultancy firm.

The Ministry of Education, Culture and Science (OCW) will act as the inquiry's commissioning party. Because animal research and the transition to animal-free innovation are relevant to the responsibilities of several ministries, a broadly constituted consultation group will be set up under the chairmanship of the OCW, whose members will include representatives of the most relevant ministries, ZonMw and NWO. The consultation group will also be involved in the policy response following the inquiry.

Follow-up process

My aim is to set up the committee over the summer. At the same time, a research firm will be appointed to support the committee. The inquiry can then start in autumn 2023. The aim is to share

the results of the inquiry and the review by international experts with the House by the end of 2024.

Minister for Education, Culture and Science,

Robbert Dijkgraaf

Establishment order, 5 December 2023

The most important passages of the establishment order are reproduced below. The full text of the order includes the committee members' declarations of interest.

(...)

Article 2. Committee on Research Involving Non-Human Primates

1. There shall be a Committee on Research Involving Non-Human Primates.
2. The committee is tasked with investigating the possibility of further reducing the number of experiments on non-human primates without affecting research strictly necessary for the control of life-threatening diseases and outbreaks of infectious diseases that threaten public health.
3. The committee will issue a report on this matter to the minister by November 2024.

Article 3. Details of the committee's duties

5. The committee is to define the terms 'life-threatening disease' and 'infectious disease that threatens public health'.
6. The committee is to investigate what scientific research with non-human primates is necessary for the control of life-threatening diseases and outbreaks of infectious diseases that threaten public health, and the conditions under which such research can be further phased out in the future.
7. The committee is to investigate the scope for entirely phasing out other scientific research with non-human primates as soon as possible.
8. The committee is to map the options referred to in the previous subtask by defining various scenarios in which the scientific, ethical, legal, economic, international and societal implications are set out.

Article 4. Composition, appointment and dismissal

1. The committee is to consist of one chair and eight other members.
2. The chair and other members shall be appointed by the minister for a term of fifteen months, which may be extended.
3. Before joining the committee, the chair and the other members shall inform the minister as to the primary and additional positions they hold and any relevant business interests they have. If the primary or additional position held by, or the relevant business interests of, the chair or any other member should change, the minister may reconsider that person's membership of the committee.
4. The chair and other members are to make their knowledge and experience available in a personal capacity, and not to act as representatives of any particular interest group.
5. The chair and other members may be suspended or dismissed by the minister at their own request or if they are deemed to be unsuitable or incompetent, or if other serious grounds exist.
6. If an individual's membership of the committee is ended while the committee's work is still in progress, the minister may appoint another member.

Article 5. Members

1. The following persons are appointed to the committee with effect from 15 November 2023, until 15 February 2025:
 - a. Prof. W.E. (Wiebe) Bijker, also chair;
 - b. Prof. A. (Annemieke) Geluk;
 - c. Prof. W.A. (Pim) van Gool;
 - d. Dr. L. (Lotte) Krabbenborg;
 - e. Prof. H.G.M. (Bert) Leufkens;
 - f. Prof. F.L.B. (Franck) Meijboom;

- g. Prof. C.L. (Christine) Mummery;
 - h. Prof. C.P. (Chantal) Rovers;
 - i. Dr. F.M.S. (Femke) de Vrij.
2. A list of the relevant primary and additional positions held by and relevant business interests of the members referred to in the first paragraph is set out in an Appendix to this order.

Article 6. Support of the committee

- 1. The minister shall arrange for a secretariat to provide the committee with practical support.
- 2. The minister shall arrange for research support to assist the committee with the performance of its duties.
- 3. The secretariat and research support shall be answerable for their activities exclusively to the chair of the committee.

Article 7. Working method of the committee

- 1. In the performance of its duties, the committee shall make as much use as possible of existing reports and research literature.
- 2. The chair shall report periodically to the minister on progress.
- 3. The committee shall determine its own working methods, taking account of the need to avoid (any appearance of) conflicts of interest throughout the committee's term of office.
- 4. The committee may be assisted by other persons to the extent necessary for the performance of its duties.

Article 8. Term

The committee shall be established with effect from 15 November 2023 for a period of fifteen months.

Article 9. Duty of disclosure

The committee shall provide the minister with any information that the minister may request. The minister may request access to business information and documents, insofar as reasonably necessary for the fulfilment of the minister's duties.

(...)

Appendix 6. Interdepartmental consultation group

The Ministry of Education, Culture and Science (OCW) acted as the inquiry's commissioning party. Because animal research and the transition to animal-free innovation are relevant to the responsibilities of several ministries, a broadly constituted consultation group was set up under the chairmanship of the OCW, whose members included representatives of the most relevant ministries and expert organisations. The consultation group will also be involved in the policy response following the inquiry.

The interdepartmental consultation group was made up of representatives from:

- Ministry of Education, Culture and Science (chair)
- Ministry of Agriculture, Fisheries, Food Security and Nature (and its predecessor)
- Ministry of Education, Culture and Science
- Ministry of Infrastructure and Water Management
- Netherlands Organisation for Scientific Research
- Netherlands Organisation for Health Research and Development

The Ministry of Economic Affairs was provided with the agendas and other documentation for all the meetings, but did not participate in them all.

The Interdepartmental Consultation Group on NHP Research met six times.

Appendix 7: Description of the international peer review process

1) Purpose of the review:

The purpose is to assess the quality of the scientific report prepared by the Bijker Committee on research involving non-human primates (NHPs). To that end, appreciation and critical feedback are required, which can contribute to the strength of the final report.

2) Bijker Committee establishment order:

- The committee is to define the terms 'life-threatening disease' and 'infectious disease that threatens public health'.
- The committee is to investigate what scientific research with non-human primates is necessary for the control of life-threatening diseases and outbreaks of infectious diseases that threaten public health, and the conditions under which such research can be further phased out in the future.
- The committee is to investigate the scope for entirely phasing out other scientific research with non-human primates as soon as possible.
- The committee is to map the options referred to above by defining various scenarios in which the scientific, ethical, legal, economic, international and societal implications are set out.

3) NHP report quality review:

Reviewers are asked to assess the quality of and provide feedback on the analysis and reasoning in the report, particularly in relation to the following points:

- (1) Animal testing status: Has the committee provided a good picture of Dutch and international trends and developments on animal experiments with non-human primates (NHP)?
- (2) Ethical debate: Has the committee provided a clear picture of the ethical debate and ethical frameworks within the Dutch context? Is there also clarity on the definition of the terms 'life-threatening disease' and 'infectious disease threatening public health'?
- (3) Importance of NHP research: Has the committee clearly identified what research with non-human primates is still needed for the control of life-threatening diseases and infectious disease outbreaks that threaten public health?
- (4) Replacement / phase-out: Has a clear understanding been given of the possibilities and feasibility of reducing and/or completely phasing out the remaining scientific research with non-human primates, and the preconditions that need to be met to achieve that phase-out? In this context, has the committee properly explored the potential of innovations (*e.g.* new approach methodology, NAM) and their acceptance?
- (5) Feasibility and effects: Has the committee convincingly identified the effects of different options for phasing out the remaining scientific research with non-human primates to zero as soon as possible on:
 - the (fundamental and applied) science and innovation strength of the Netherlands?
 - the number of remaining non-human primates and their welfare in European and

international perspective?

- the Netherlands' strategic autonomy and (competitive) position within Europe (e.g. for vaccine development)?

- (6) Do the scenarios proposed by the committee collectively provide a good and balanced overview of the policy options, including ethical, legal and societal implications?

The report's Appendix containing the analysis of the international literature does not need to be assessed as such; however, it is necessary to assess how the report uses this literature analysis.

4) Reviewer profiles

To get a thorough picture of the expertise needed, it is desirable for ZonMw and NWO to have access to the report or for the committee to provide a clear summary of the report's subject matter and the fields of expertise to be covered. It may then be necessary to prioritise the relevant fields of expertise, with distinction between strictly necessary and desirable fields, so that the total number of reviewers can be limited.

Given the intended purposes of the review, the proposal is to seek a minimum of six and a maximum of ten external reviews from experts in a range of fields, including the following:

- Immunology
- Virology
- Vaccinology
- Infectious diseases
- Neurology
- Animal testing procedures
- Activities of regulatory bodies (EMA, FDA)
- (Pharmaceutical) industry
- New approach methodologies (NAMs)
- Ethics

With a view to ensuring that a variety of perspectives are acquired, international reviewers with different professional backgrounds (science, industry, patients associations, etc) and from various parts of the world will be sought. It is important to avoid the reviews being coloured by strong personal support for or opposition to scientific research using non-human primates. Therefore, where possible, ZonMw and NWO will check whether potential reviewers have expressed views on NHP research in the public domain. Given that the use of non-human primates is a sensitive topic, about which almost everyone has a strong opinion, care will be taken to strike a balance between reviewers with (potential) affinity with one side of the ethical debate or the other.

Because reviewing an inquiry report of this type is not part of an academic's normal duties, ZonMw and NWO propose to offer the reviewers an honorarium based on standard NWO/ZonMw attendance fees for three half-days. Reviews may also be sought from non-academic experts whose normal work does not include reviewing reports of the relevant type.

5) Prerequisites

- Anonymity of reviewers is guaranteed.
- Reviewers have no personal interest in the committee or the outcome of the inquiry, as referred to in NWO and ZonMw's Personal Interests Code.
- Reviewers receive an honorarium for providing a thorough review, based on a time input of three half-days.

- Reviewers suggested by the committee and interdepartmental consultation group will be considered, but ZonMw and NWO reserve the right to invite other reviewers in order to safeguard the process and its independence.

6) Process and timeline

In November and December, ZonMw and NWO will seek to identify suitable reviewers who can be approached once it is possible to provide them with a specific timeframe. The Bijker Committee intends to deliver the NHP report by 10 December. ZonMw and NWO will be given a provisional delivery date for the English translation as soon as possible; it is suggested that the Bijker Committee confirms at least six weeks before the delivery of the English translation that the deadline will be met, so that reviewers can be contacted with the relevant information.

Once a final date for delivery of the English version of the report is known, ZonMw and NWO will start writing to potential reviewers. Potential reviewers will be asked to provide ZonMw and NWO with reviews within the timeframe set out below.

The incoming reviews will be scrutinised by ZonMw and NWO. Although ZonMw and NWO will seek to forward the reviews to the Bijker Committee in the most unedited form possible, scrutiny is required in order to ascertain that the reviews are anonymous and complete. If a review is considered to lack sufficient substance or to contain information that could identify the reviewer, ZonMw and NWO may contact the reviewer to ask for changes and/or clarification.

General timeline

October - December	The Bijker Committee suggests reviewers to ZonMw and NWO; ZonMw and NWO draw up a list of potential reviewers.
6 weeks before delivery	Approach potential reviewers
0-2 weeks after delivery	Reviewers are given two weeks to submit their reviews.
2-3 weeks after delivery	ZonMw and NWO scrutinise reviews to check anonymity and completeness and, if necessary, contact reviewers with questions or to seek changes.

The Christmas holiday period may fall within the timeframe outlined above, in which case the review process will need to be extended. In that scenario, a delay of at least two weeks should be expected. If the period when reviewers would be asked to submit their reviews on the basis of the timeline presented above falls in the Christmas holiday period, NWO/ZonMw will start approaching potential reviewers as scheduled, but will allow the reviewers an additional two weeks to complete their reviews.

Appendix 8. Committee's response to the reviews

To: Interdepartmental consultation group on NHP research
From: Committee on Research involving NHPs
Re: Committee's response to the reviews
Date: 10-1-2025

The committee has received twelve anonymised reviews from ZonMw/NWO (see [appendix 7](#) for details of the review process). Each review was three to six pages in length.

The committee's response to the reviews is set out below for the benefit of the interdepartmental consultation group on NHP research, the body formally responsible for commissioning the international peer review.

General impression

The committee is very happy with the reviewers' work – in a relatively short period around Christmas and New Year, they have studied the draft report and provided their views. All the reviews exhibit a high level of engagement with the issue of NHP research, even though the reviewers differ significantly in their judgements. The reviews address all the questions posed in the review-protocol; many reviewers make concrete suggestions regarding changes and clarifications; and some reviewers draw the committee's attention to additional literature.

In general, the reviewers are positive about the quality of the report. Reviewer #9 being the one exception. The committee believes that reviewer #9's negative assessment is attributable, at least in part, to the reviewer regarding the supplementary literature review presented in [Appendix 1](#) to the report as the principal basis of the report – that assumption is incorrect, as the committee explains again below (themes 1 and 5). The reviewer in question was also critical of the committee for focusing primarily on the Dutch research, which is basic and translational research, and therefore paying less attention to the regulatory research carried out in other European and non-European countries. The committee took that approach because its remit was to conduct a survey of *Dutch* NHP research.

Not all the reviewers consider the report to be entirely neutral and balanced. Some of them perceive there to be an implicit bias in favour of NHP research on the part of the committee (reviews #1 and #6), while others perceive there to be an implicit bias against such research (reviews #4 and #7). There are also reviewers who explicitly state that they found the report to be balanced (reviews #8 and #10). The committee expressly sought to present the most balanced possible analysis, and not to imply any preference for any one policy scenario. The committee has therefore used every instance of perceived bias as a starting point for removing any suggestion of preference on its part, and to present the policy scenarios in the most balanced manner possible.

Feedback incorporated by the committee

The reviewers' comments can be divided on the basis of the themes to which they relate. The committee explains below how it has acted on the feedback received on each theme individually.

1. Methodology

The committee's methodology was apparently not entirely clear to all the reviewers (reviewers #3, 6, 7, 9). A new section headed 'Methodology and work process' has accordingly been added to the introduction. The new section emphasises that the report has two primary bases: a literature review by the committee and interviews that the committee held with experts. The PubMed-based bibliographical analysis of international publications (see below) merely provided supplementary information.

2. "Life-threatening" or "life-threatening and otherwise serious"

Several reviewers (#1, 2, 3, 6, 8) explicitly endorse the committee's view that there is no clear scientific basis for drawing a distinction between 'life-threatening' diseases and 'non-life-threatening' diseases. The committee has clarified the relevant passages of the report, and has explained why use of the phrase 'unmet medical needs' does not constitute a solution.

3. COVID vaccine development and NHP research

The development of SARS-CoV-2 vaccines is an important feature of the report, partly because the Netherlands' pandemic preparedness was a central element of the committee's assignment. The role that NHP research played in the development of such vaccines was not made sufficiently clear (reviewers #1, 3, 5, 7, 12). The way that the BioNTech/Pfizer and Moderna vaccines were developed is particularly important to an understanding of the role of NHP research in vaccine development, because less NHP research than usual was done for those vaccines. Nevertheless, NHP experiments did form part of the development process. The committee has clarified the relevant passages of section 2.1.1 and added a number of references to scientific publications.

4. Ethical discussion

Most of the reviewers were positive about the ethical discussion. Nevertheless, in response to various comments (reviewers #1, 3, 4, 5, 6, 9, 11, 12), the committee has fleshed out the discussion of the ethical frameworks and clarified it with additional references. Further, more attention has been given to the special status of NHPs, to care ethics, and to the role that ethics play in influencing the choice of a policy scenario.

5. Nature, value and limitations of Gallant's literature review in [appendix 1](#)

The purpose and methodology of the supplementary bibliographical analysis of international literature in PubMed carried out by Dr. James Gallant were evidently not made sufficiently clear (reviewers (#1, 5, 6, 9, 12)). In its introduction to Appendix 1, the committee has accordingly clarified the nature, value and limitations of the literature review. A number of clarifications have also been made to the reporting of the analysis in Appendix 1.

6. Table 4 regarding NAMs

In [Table 4](#) of the report, the committee presents its assessment of when the various NAMs are likely to be sufficiently mature to make NHP research unnecessary. Various reviewers suggested that the estimated timescales were not adequately justified (reviewers #7, 9). The committee based its estimates on its consultations with NAM researchers. The committee has now added a number of references to support its estimates.

7. Other diseases, basic research

Some reviewers suggested that the report did not provide enough examples of 'other and basic scientific research' with NHPs, i.e. research other than that into pandemic infectious diseases and

life-threatening and otherwise serious diseases (reviewers #3, 4, 5, 7, 12). The committee has accordingly added a number of examples of neuroscientific and cardiovascular research, and has fleshed out the TB case study.

8. Policy scenarios

Various changes have been made so that the four policy scenarios are more precisely described and more clearly explained (with thanks to reviewers #1, 7, 11). The four policy scenarios are presented to indicate the spectrum of policy options regarding which political choices must now be made. While the committee can imagine that democratic experiments such as citizens' councils could play a role in that context (reviewer #5), the committee considers the detailing of such processes to be outside its remit.

9. Clarification of arguments

The arguments presented by the committee have been clarified at various points throughout the report. The following are a few examples:

- The four types of NHP research permitted under the EU's Animal Experiments Directive have been made more explicit (reviewer #9)
- The four types of NHP research distinguished in the EU directive have been explained more clearly (reviewer #9)
- The special status that NHPs have, relative to other laboratory animals, has been made more explicit (reviewer #10)
- The assessment order that must be followed by law – first considering whether a research question can be answered using NAMs and without NHPs, and proceeding to set up an NHP experiment only if the outcome of the first assessment is negative – has been made more explicit in the policy scenarios (reviewer #11)
- The circumstances under which animals are housed at the BPRC have been described more fully (reviewer #5)
- The structure of the arguments presented in Chapter 2 has been made clearer (reviewer #5)
- The meaning of the abbreviation NAM ('new approach methodology', and not 'non-animal model') has been made more explicit (reviewer #7)
- Another example of the relevance of NAMs for pharmacokinetic research has been added (reviewer #6)
- The passage regarding the use of NHPs or NAMs has been clarified (reviewer #11)
- The fact that transparency and good public communication are important in all policy scenarios has been stated more clearly (reviewer #9)
- The reference to the committee members' declarations of interests has been clarified (reviewer #12)

Declined suggestions

The committee has not acted on all the suggestions made by the reviewers.

- The committee has not provided a quantitative summary of successful and unsuccessful NHP experiments, because it is not possible to do so in a non-controversial manner (reviewer #5)
- The committee has not developed a roadmap for the introduction of NAMs because it lacks the expertise necessary to do so (reviewer #5)
- The committee has not added any specific policy recommendations, because doing so would be inconsistent with its remit (reviewer #5)

- The committee has not provided a more detailed description and evaluation of the NHP research conducted by various groups in the Netherlands, because that is outside its remit (reviewer #7)
- The committee has confined itself to NHPs as far as possible, and has not extended its analysis to all animal research (reviewer #7)
- In [appendix 2](#), the committee has not provided detailed profiles of the experts it consulted, because, in their discussions with the committee, all of them drew upon broader and richer experience than that gained through their original training (reviewer #7)
- The committee has not provided additional quantitative data from the ALURES database, because that would add little to the committee's analysis, and because the database is not accessible to everyone (reviewer #9)
- The committee has not added a detailed explanation for the growth of NHP research in countries such as China and the US, because the general reasons are already given, and because the committee is not in a position to properly investigate the situation in countries other than the Netherlands (reviewer #11)
- The committee has not added a detailed timeline for the development of various NAMs and the resulting replacement of NHP experiments, because that would be outside its remit (reviewer #12)
- The committee is unable to provide a detailed quantification of the various dimensions of the policy scenarios, because it has insufficient time and resources to do so (reviewer #12)
- The committee is unable to add concrete case studies of NAM development, because it has insufficient time and resources to do so (reviewer #12)