ANNE VAN VEEN

OF MICE, MONKEYS & BETTER SCIENCE

NONHUMAN ANIMAL EXPERIMENTATION
AND ITS ALTERNATIVES IN THE NETHERLANDS (1950-2020)

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NONHUMAN ANIMAL EXPERIMENTATION AND ITS ALTERNATIVES
IN THE NETHERLANDS (1950-2020)

OVER MUIZEN, APEN EN BETERE WETENSCHAP

EXPERIMENTEN OP NIET-MENSELIJKE DIEREN EN ALTERNATIEVEN
DAARVOOR IN NEDERLAND (1950-2020)

(met een samenvatting in het Nederlands)

Proefschrift

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To Koko and Yum Yum

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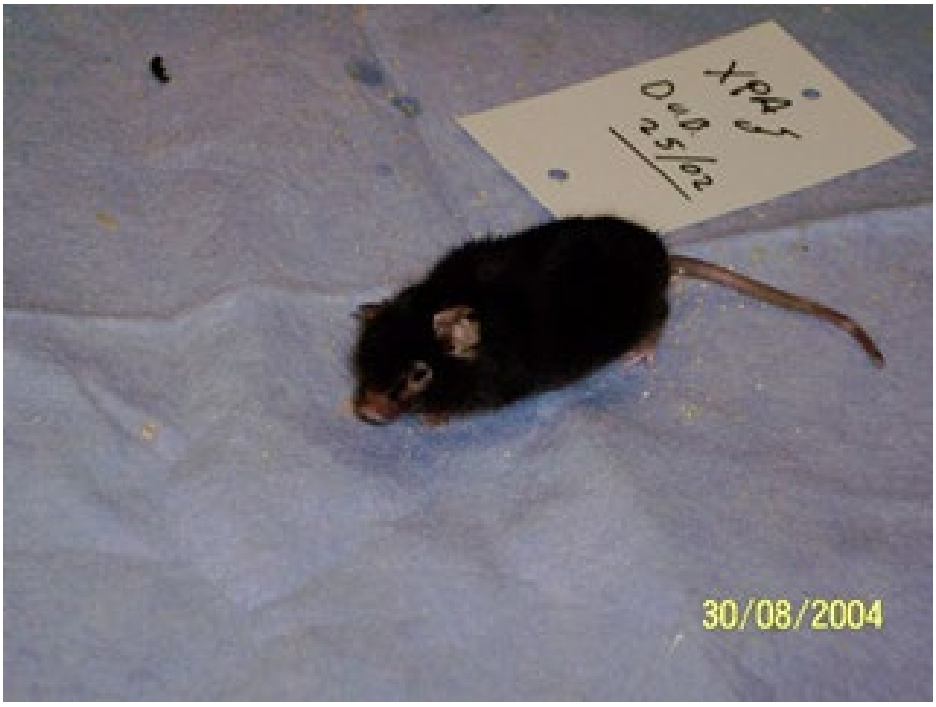

Figure I.1 An XPA-mouse. Source: RIVM

The mouse in this picture was born on February 25, 2004 in Bilthoven, the Netherlands, in one of the animal rooms of the Animal Research Centre used by the National Institute of Health and Environment (RIVM). She is not a 'regular' mouse but an XPA-knockout mouse. This means that the XP-A genes in her DNA are inactivated; they have been 'knocked out'. As a consequence, she is deficient in DNA-repair and therefore more likely to develop tumors when exposed to carcinogens. In the picture, she is six months and five days old. If you look closely at her left ear, you can see that a few pieces of the ear have been cut away. This was done to mark the mouse so that she could be distinguished from other mice living in the same cage. During her life in the laboratory, she was used in experiments. Like most XPA-mice living in laboratories, she was eventually killed by a human being.

I choose to open this thesis with a picture of this mouse to immediately draw your attention to her as an embodied individual. I could have written a thesis on nonhuman animal experimentation without writing about any of the nonhuman animals tested upon as individuals. I have instead chosen to aim for a thesis that 'decenters the human' by writing multispecies histories in which nonhuman animals are subjects with their own histories, worthy of investigation in their own right.

The mouse in the image is therefore but one of several nonhuman animals that you

will meet in the following chapters and into whose lives I hope to give insight. The nonhuman animals that you will encounter are only a very small percentage of the nonhuman animals that have been tested upon in the Netherlands between 1950 and 2020—the area and period of focus of this thesis. Since registration started in 1978, 34,773,113 nonhuman animal experiments have been registered.[1] This number only includes nonhuman vertebrates and, since 2014, cephalopods; nonhuman animals of other species such as fruit flies are commonly used in experiments but are not counted.[2] Compared to many other groups of nonhuman animals, especially free-living nonhuman animals, the lives of these tested nonhuman animals have been highly controlled by humans, both directly and indirectly. There are, for example the scientists that designed experiments as well as scientists who—sometimes successfully and sometimes not—developed alternatives to nonhuman animal testing. Animal technicians performed the experiments and controlled the breeding, housing, feeding and dying of the nonhuman animals living in laboratories. Legislators dictated what was and was not allowed in nonhuman animal testing, but also required certain experiments through their legislation. Members of Animal Experiments Committees meanwhile determined the permissibility of individual experiments. Activists demanded freedom for the tested animals or at least better living conditions and more investments in alternative methods. Thus, to understand past nonhuman animal testing practices and the experiences of the nonhuman animals who have been tested upon, these human actors need to be included in the story as well but in a manner that does not push other animals to the margin of the histories being told.

Mice and other nonhuman animals that are tested on in laboratories are often written about in aggregate numbers or reduced to identification by the genetic characteristics of their strain.[3] Although there has recently been more attention given to nonhuman animals in history, these animals still generally do not take center stage.[4] In research on the history of medicine specifically, Woods notes that even though nonhuman animals are increasingly part of medical history in the 21st century, they usually only feature in the margins rather than being investigated as subjects in their own right. This leads

1 This includes all years from 1978 until 2019, except for 1979, since there is no registration for that year. Veterinaire Hoofdinspectie van de Volksgezondheid. Sectie Dierproeven and Nederlandse Voedsel- en Warenautoriteit., 'Zo doende ...: jaaroverzicht door de Sectie Dierproeven van de Veterinaire Hoofdinspectie van de Volksgezondheid over het jaar ...', series 1978-2021.

2 For a study on fruit fly-human relations in the laboratory, see Tara Mehrabi, 'Queer Ecologies of Death in the Lab: Rethinking Waste, Decomposition and Death through a Queerfeminist Lens', Australian Feminist Studies, 35.104 (2020), 138–54 <https://doi.org/10.1080/08164649.2020.1775068>.

3 Lynda Birke, Mette Bryld, and Nina Lykke, 'Animal Performances', Feminist Theory, 5.2 (2004), 167–83 <https://doi.org/10.1177/1464700104045406>; Gail Davies, 'Mobilizing Experimental Life: Spaces of Becoming with Mutant Mice', Theory, Culture & Society, 30.7–8 (2013), 129–53 <https://doi.org/10.1177/0263276413496285>; Karen A. (Karen Ann) Rader 1967-, Making Mice: Standardizing Animals for American Biomedical Research, 1900-1955 (Princeton: Princeton University Press, 2004).

4 Etienne Benson, 'Animal Writes : Historiography, Disciplinarity, and the Animal Trace', Making Animal Meaning, 2011, 3–16; Harriet Ritvo, 'On the Animal Turn', Daedalus, 136.4 (2007), 118–22; Anita Guerrini, 'Deep History, Evolutionary History, and Animals in the Anthropocene', in Animal Ethics in the Age of Humans: Blurring Boundaries in Human-Animal Relationships, ed. by Bernice Bovenkerk and Jozef Keulartz, The International Library of Environmental, Agricultural and Food Ethics (Cham: Springer International Publishing, 2016), pp. 25–37 <https://doi.org/10.1007/978-3-319-44206-8_2>.

to anthropocentric histories that are not as rich as they could be.[5] Historians working within what has been called 'the animal turn' are developing ways of writing history that move beyond anthropocentrism, not only to do justice to past nonhuman animals, but also as a starting point for rethinking present and future interspecies relations.

Scientists have termed the present historical age the Anthropocene, and human dominance over nonhuman animals is an important aspect of this. Interspecies relations as they currently stand are problematic, not just for the many nonhuman animals currently harmed by humans, but also for humans who (will) suffer the consequences of the Anthropocene— as the fate of many, from climate refugees to COVID-19 victims, is already demonstrating.[6] This is why historian Anita Guerrini has argued that the Anthropocene calls for a radical decentering of the human in history. Writing animal histories that radically decenter the human will enable us to 'deconstruct the animal-human divide and begin to write a new history that can underpin a new ethics for the Anthropocene'.[7]

The first aim of this thesis it to contribute to this decentering, making this project relevant to the very broad challenges we face today. Secondly, the thesis aims to contribute more specifically to tackling the 'wicked problem' of replacing nonhuman animal testing by nonanimal alternatives.[8] Even though there has been agreement among researchers (and virtually everyone else) for a long time that it would be preferable for us to stop testing on other animals, it is still common practice today. Indeed, most Dutch researchers do not believe we will be able to end nonhuman animal testing anytime soon, if at all.[9] Since the 1980s, efforts have been made to develop alternatives, but the validation and regulatory acceptance of these alternatives have been problematic.[10] Even when alternatives are eventually adopted, the process can take up to eleven years.[11] I do not pretend to present a solution to this 'wicked problem' in this thesis,

5 Abigail 1972- Woods and others, Animals and the Shaping of Modern Medicine: One Health and Its Histories, Medicine and Biomedical Sciences in Modern History, 1 online resource (xvii, 280 pages) : illustrations vols (Cham: Palgrave Macmillan, 2018) <http://doi.org/10.1007/978-3-319-64337-3> [accessed 23 February 2021].

6 Charlotte E. Blattner, 'De Zoonosis a Zoopolis', Derecho Animal. Forum of Animal Law Studies, 11.4 (2020), 41–53 <https://doi.org/10.5565/rev/da.524>. It is important to note here that the concept of the Anthropocene is not unproblematic and that there is inequality among humans, both when it comes to suffering the consequences and to having taken part in causing the Anthropocene. See: Kathryn Yusoff, A Billion Black Anthropocenes or None, Forerunners: Ideas First from the University of Minnesota Press, 1 online resource (xiv, 115 pages): illustrations vols (Minneapolis, MN: University of Minnesota Press, 2018).

7 Guerrini, Deep History, 26.

8 M. J. W. A. Schiffelers, 'Animal Testing, 3R Models and Regulatory Acceptance: Technology Transition in a Risk-Averse Context', 2016 <http://dspace.library.uu.nl/handle/1874/334103> [accessed 19 December 2016], 15-16. Schiffelers argues that the regulatory acceptance of alternatives to nonhuman animal testing has many characteristics of a wicked problem, a problem that is difficult to define and solve, for example: involvement of many different stakeholders, a multilevel playing field across different sectors, institutes and geographies, multi-causality, and conflicting objectives.

9 S. Bressers and others, 'Policy Driven Changes in Animal Research Practices: Mapping Researchers' Attitudes towards Animal-Free Innovations Using the Netherlands as an Example', Research Integrity and Peer Review, 2019 <https://doi.org/10.1186/s41073-019-0067-5>.

10 Schiffelers, Animal Testing; Kristina Wagner, Bettina Fach, and Roman Kolar, 'Inconsistencies in Data Requirements of EU Legislation Involving Tests on Animals', ALTEX - Alternatives to Animal Experimentation, 29.3 (2012), 302–32 <https://doi.org/10.14573/altex.2012.3.302>.

11 Wagner, Inconsistencies, 304.

but the historical analyses of (un)successful development and implementation of alternatives can provide insights that are useful for the present situation. Additionally, the multispecies approach taken here provides a fresh perspective that is generally not included when looking at alternatives to nonhuman animal testing from a transition studies perspective. Thirdly, the thesis makes a historiographic contribution by taking a multispecies approach and focusing on histories of nonhuman animal testing and alternatives in the Netherlands between 1950 and 2020, into which not much research has been conducted. The gap in the literature which this thesis aims to fill will become clearer in a discussion of the historiography of nonhuman animal testing. This is followed by a discussion of the sources I used and the structure of the thesis. First however, I will describe my research questions and case studies.

RESEARCH QUESTIONS AND CASE STUDIES

This research project was initiated by the Dutch National Institute of Public Health and Environment (RIVM) in 2015. The RIVM wanted a historical study into the use of nonhuman animal testing and alternatives at their own institute, situated within an (inter) national context. To ensure independence, they asked Utrecht University to conduct the research and an independent 'sounding board' committee was formed to advise on the thesis. The members of this committee were: Dr. Saskia Arndt, Professor of Animal Behavior at Utrecht University and Dr. Marie-Jeanne Schiffelers, Associate Professor & Senior Advisor at Utrecht University School of Governance. Prior to the start of this PhD project, a very general research question was agreed upon by UU and the RIVM:

> How did practices of nonhuman animal experimentation and its alternatives develop in the Netherlands, and at the RIVM in particular, in the period between 1950–2020?[12]

This question leaves plenty of room for qualification and specification and does not yet reflect the research aims of my thesis. Central to this thesis is not only the question of which developments have taken place, but specifically the question of what these developments have meant for the experiences of different nonhuman animals in different time periods. What has changed for tested animals? What has remained the same? How have developments in law, science, politics, and society affected the lives of nonhuman animals and laboratory interspecies relations and vice versa?

The initial research question is also very broad in scope: to include in this thesis all nonhuman animal experiments and alternatives between 1950 and 2016 in the Netherlands—or even just at the RIVM—would have been impossible. I therefore focus on three case studies: the RIVM Polio-monkeys, the RIVM animal experiments committee, and the XPA-mice. In addition, I have written a chapter describing more general developments between 1950 and 2020 in law, science, society, and politics in relation to nonhuman animal testing and alternatives in the Netherlands.

These case studies have been selected for a variety of reasons. First of all, they are cases in which the RIVM has played an important role (inter)nationally and are there-

12 Originally, the research question read 'in the period between 1950-2016', but this has been changed to 1950-2020 so that the thesis includes the most recent developments as well.

fore relevant beyond the history of the institute alone. Secondly, they have been chosen based on the availability of sources about the micro-level of life and work at the laboratory (e.g., the availability of images of the nonhuman animals involved, see Sources for more details). This made it possible to provide thick descriptions of the lived experiences of animals (human and nonhuman) and their interactions, allowing for a balance between zooming in on the micro-level of the animal lab and zooming out to look at structural forces and broader developments. In addition, these cases provided the opportunity to include and take a closer look at several issues and developments that sparked public debate: the use of primates, the use of transgenic techniques, the issue of 'higher and lower' animals (i.e., monkeys vs. mice), and questions of ethics and legislation. Together, these examples also range over the entire time period of 1950–2020 and give examples of successful and unsuccessful development and implementation of testing alternatives.

HISTORIOGRAPHY

Historical scholarship about nonhuman animal experimentation in the Netherlands is rare. If you conduct a Google Scholar search to find historical articles on nonhuman animal testing in the Netherlands, you come up empty handed. Expanding the search to include books yields a few results. Smit wrote a short book on the 'hundred years of debate' about nonhuman animal testing in the Netherlands and Van der Gulden & Van Gaalen wrote about the development of Laboratory Animal Science (*proefdierkunde*) in the Netherlands.[13] These books, written by a biologist and by veterinarians, respectively, cannot however be considered historical scholarship. A study that *is* based on historical research is Amanda Kluveld-Reijerse's PhD thesis on the history of anti-vivisectionist organizations and their expressive politics in the Netherlands in the period between 1890–1940.[14] Although it focusses on anti-vivisectionism rather than nonhuman animal testing itself (and on an earlier time period than this thesis), Kluveld-Reijerse's work has been instructive in providing a nuanced understanding of activists and their relation to science and politics. Kluveld-Reijerse shows that anti-vivisectionists and pro-vivisectionists are not as diametrically opposed as they are often portrayed to be and that they often share beliefs about science and politics.[15] She also warns against valuing instrumentality over expressivity or adopting too narrow a conception of politics, both of which may exclude or devalue the work of women activists.

Looking beyond the discipline of history, additional recent work dealing with nonhuman animal testing and alternatives in the Netherlands can be found. Most notable are the PhD theses of Meggie Pijnappel and Marie-Jeanne Schiffelers, both written from a policy research perspective.[16] Pijnappel's thesis focuses on a discourse analysis of poli-

13 Cock Smit, Dierproeven: 100 jaar discussie (Kampen: La Rivière en Voorhoeve, 1989); Ontwikkeling van de Proefdierkunde in Nederland., ed. by Gulden, W.J.I. van der & Gaalen, J.M. van (Eds.), 1997.

14 Amanda Alwien Kluveld-Reijerse, Reis door de hel der onschuldigen: de expressieve politiek van de Nederlandse anti-vivisectionisten, 1890-1940, Geschiedenis en gezondheid (Amsterdam: Amsterdam U.P, 2000).

15 Kluveld-Reijerse, Reis door de hel, 220.

16 Schiffelers, Animal Testing; M. C. Pijnappel, Lost in Technification : Uncovering the Latent Clash of Societal Values in Dutch Public Policy Discourse on Animal-Testing Alternatives ([S.l. : s.n.], 2016) <https://repository.ubn.ru.nl/handle/2066/151524> [accessed 4 May 2019].

cy and legal text on alternatives to nonhuman animal testing. It is not a historical study per se, but it does cover a large time period, namely 1970–2011. Pijnappel's research has been very useful in that it provides an analysis of how the meaning of 'alternatives' has changed over time, identifying four 'frame shifts' in Dutch policy discourse on testing alternatives: 'regulating animal research' (1970–1977), 'stimulating the 3Rs' (1984–1985), 'growing public discontent' (1992–1995), and 'integrating science, innovation & animal welfare' (2008–2011).[17] Schiffelers' thesis also focuses on alternatives but does so from a transition studies perspective. She asks what the drivers and barriers are to the regulatory acceptance of alternatives to nonhuman animal testing and finds that risk-aversion is a major barrier to moving away from nonhuman animal testing in the regulatory field. Both these theses emphasize the 'wickedness' of the issue of nonhuman animal testing, showing that technical innovations have not and will not provide a simple solution (hence the title of Pijnappels thesis: 'Lost in Technification'). The two authors both underscore the importance of including societal values in analyses of practices of nonhuman animal testing and alternatives, such as values relating to public health risks and nonhuman animals.

After this short overview of research on nonhuman animal testing and alternatives in the Netherlands, it can be safely concluded that the subject is under-researched and that historical, multispecies approaches are completely absent. The work that exists does not focus on nonhuman animal testing practices themselves, let alone on tested animals, but on related subjects. What about international literature? Is there historical work on nonhuman animal testing practices in other countries and, if so, to what extent might these be multispecies histories?

Catherine Duxbury finds that historical research on nonhuman animals is often written by non-historians from an animal studies perspective and often lacks historical depth (e.g., because of the lack of primary sources).[18] In her dissertation, Duxbury writes about military nonhuman animal experimentation in the UK in the 1960s and finds that not much has been written about this time period. What has been written tends to focus on the US or on anti-vivisectionism rather than on animal testing.[19] Research that has been more focused on specific groups of laboratory animals in specific time periods and places include those of Karen Rader, Robert Kirk, and of Duxbury herself. Rader's well-known book *Making Mice* tells the story of the Jackson Laboratory and its production of inbred mice in the period 1900–1955.[20] Through the lens of this particular story, the book also tells the more general story of important developments in the field of biology during this period, focusing on practices of standardization. In her work, Rader recognizes the mice who were experimented on as historical actors who played an active part in scientific knowledge production.[21]

Kirk meanwhile wrote several historical pieces on (care for) laboratory animals in

17 Pijnappel, Lost in technification, 80.

18 Catherine L. Duxbury, Animal, Gender and Science: Animal Experimentation in Britain, 1947-1965, 2016 http://repository.essex.ac.uk/19887/1/Thesis%20Final.pdf [accessed 24 May 2018].

19 For example Richard D. French, Antivivisection and Medical Science in Victorian Society (Princeton University Press, 2019); Bruno Atalić, 'Historical Development and Ethical Considerations of Vivisectionist and Antivivisectionist Movement', Jahr : Europski Časopis Za Bioetiku, 3.2 (2012), 399–414; Nicolaas A. Rupke, Vivisection in Historical Perspective (London: Croom Helm, 1987).

20 Rader, Making Mice.

21 Rader, Making Mice, 20.

the UK.[22] His work gives more space to nonhuman agency, embodiment, and subjectivity and can also be placed in the STS body of literature that has focused on care and the co-constitution of human and nonhuman animal bodies in the laboratory. Duxbury's work is a rare example of historical literature that is explicitly committed to writing non-anthropocentrically about nonhuman animal experimentation. In her thesis, she draws on feminist science studies as well as critical animal studies and posthumanism to show how a historical approach can benefit from being inspired by these theories, but also makes an important contribution by staying committed to the historical method of using primary sources and making connections between broader trends and specific individuals, times, and places.

Rader, Kirk, and Duxbury are all examples of scholars working within the 'animal turn' in history. They are also clearly all influenced by disciplines outside of history as I am myself, recognizing how other disciplines can be instructive in writing multispecies histories. This does not mean that all theoretical positions of scholars working within the animal turn are the same; perspectives on key concepts such as (nonhuman) agency and power vary significantly. Compared to the work of Rader and Kirk, for example, both my own work and that of Duxbury focus much more on interspecies power inequalities and their consequences for nonhuman animals. Rader states for example that the mice who were tested upon had no voice, whereas I would argue that they had voices but that their voices were often not acknowledged (at least not beyond a basic expression of, for example, pain) due to extremely asymmetrical power relations.[23] Although the theoretical approach of Duxbury is similar to my own, an important difference (besides time period and location studied) lies in my choice to focus on the lives and experiences of two specific groups of nonhuman animals.

These differences between scholars working within the animal turn will become clearer in Chapter 1. There are several disciplines and theoretical approaches within these disciplines that can provide useful analytical tools for decentering the human in historiography. Likewise, many intricacies need to be detailed to clarify what I mean by writing a multispecies history that decenters the human. Therefore, I have devoted a separate chapter to the theoretical framework I used and how this framework has affected the questions I asked and the methods I chose.

SOURCES

The research questions I have posed require an analysis of the past which includes different perspectives and levels of analysis. Such an analysis required that I examine

22 For example: Robert G. W. Kirk, 'A Brave New Animal for a Brave New World: The British Laboratory Animals Bureau and the Constitution of International Standards of Laboratory Animal Production and Use, circa 1947–1968', Isis, 101.1 (2010), 62–94 <https://doi.org/10.1086/652689>; Robert G. W. Kirk, 'Recovering The Principles of Humane Experimental Technique: The 3Rs and the Human Essence of Animal Research', Science, Technology, & Human Values, 43.4 (2018), 622–48 <https://doi.org/10.1177/0162243917726579>; Robert G. W. Kirk, 'Care in the Cage: Materializing Moral Economies of Animal Care in the Biomedical Sciences, c.1945-', in Animal Housing and Human-Animal Relations: Politics, Practices and Infrastructures, ed. by Kristian Bjørkdahl and Tone Druglitrø, Wellcome Trust–Funded Monographs and Book Chapters (Oxon (UK): Routledge, 2018) <http://www.ncbi.nlm.nih.gov/books/NBK539323/> [accessed 23 February 2021].

23 Rader, Making Mice, 20.

a variety of sources, ranging from legislative texts to objects such as cages. Since this research focuses on case studies of nonhuman animal testing and alternatives at the RIVM, *the RIVM Archive* was the most logical starting point. For each of the case studies, I searched the RIVM archive catalogue with relevant keywords. Although I read all files which seemed relevant based on this search, there were some indications that additional relevant files may have been missed. Some files were mislabeled and many were labeled simply with 'polio' without any further description. During the analysis of the files on the Animal Experiments Committees, I found a file on the Polio-monkeys which had not emerged when using the search terms polio or monkey(s). In addition, some of the files that appeared in the search had already been destroyed. Other documents from the RIVM had been moved to *the National Archive*, and thus I consulted those files there. A wide variety of RIVM documents had been archived. There were many documents, including minutes of meetings, yearly reports, and other official documents, which were very helpful in creating a timeline. There were also documents that gave more insight into interactions between individuals and the daily world of the laboratory, such as maps of animal stables, lab journals, and email correspondence.

To gain a deeper understanding of the daily world of the laboratory, *the RIVM image bank* and *(historical) objects and places* were instrumental sources. The RIVM image bank contains a great deal of images of nonhuman animals who were used for experimentation, including the monkeys and mice I studied in this thesis. For the Polio-monkeys in particular, there were many stored images which covered a large time period. There were not many images of the XPA-mice in the image bank, but I obtained additional images via respondents. To give myself an even more embodied understanding of the world of past tested animals, I visited the Animal Research Center where they had lived several times. Although the facility has undergone many changes over the years, some of the animal rooms have remained the same and many disused cages were still present for me to see and touch.

As the case studies I utilize are fairly recent, it was possible to conduct *interviews* with several respondents for each of the cases. These respondents were selected based on their specific experiences, with the aim of including different perspectives (both of researchers and of animal technicians). Still, although I was able to include different perspectives through these interviews, I did not aim to be exhaustive with the selection I made, nor have respondents' answers served as representative of a larger group. Availability and willingness to participate of course also played a role in the selection.[24]

The final source I used which originated from the RIVM were *published articles* by RIVM researchers and animal technicians. These articles often provided information on experimental procedures that had been used, but were also interesting in analyzing how nonhuman animals who had been tested upon featured in different types of documents across different time periods.

To include the perspective of 'the public', and specifically activist members of the public, I drew on newspaper articles, articles written by activists in journals, and some documents from the *Proefdiervrij archive*. In addition, I used secondary sources, such as studies on public opinion of nonhuman animal testing. Secondary sources also provided (international) context. To further understand the political, policy, and legislative contexts, I made use of policy documents, legal texts, and transcripts of debates in the Dutch Parliament.

Most of the sources I have quoted from were originally in Dutch; all translations into

24 See 'Literature and Sources' for a list of interviews.

English are my own. Whenever certain words were difficult to translate or dual meanings may have been lost in translation, the Dutch word is provided in parentheses. In the methods section in the next chapter, I will elaborate on how I used these sources and why I used them in these ways.

STRUCTURE

This thesis consists of six chapters, a conclusion, and an epilogue. I have ordered them in the way that makes most sense to me, but since each chapter is self-contained you can also choose to read them in a different order if you prefer.

The first chapter deals with the theoretical framework and methods employed in this thesis. It gives an overview of the different theoretical approaches that affected the thesis. I describe these approaches, how they relate to one another, and how they shaped my own theoretical vantage point and the thesis you are reading now. I likewise explain why I chose certain case studies and the focus points within these cases, and I make clear what my theoretical approach meant for the methods I used.

Chapter 2 is the first empirical chapter of the thesis and asks the question: how did nonhuman animal experimentation and alternatives develop over time in the realms of law, Laboratory Animal Science, society, and politics in the Netherlands between 1950 and the present? I sketch broad trends as well as specific developments at the RIVM across three time periods. I also reflect on the question of what these developments have meant for nonhuman animals: what has changed for them and what has remained the same? What did humans find acceptable as scientific practices of using nonhuman animals during these three time periods? This chapter answers its own questions but also provides the backdrop for the following chapters in which we zoom in on three specific cases.

You will meet the 'Polio-monkeys' of the RIVM in Chapter 3. The RIVM has been responsible for the production of the polio vaccine since vaccination first started in the Netherlands in the 1950s. To produce the vaccine, RIVM used the kidney cells of these monkeys. Initially, the monkeys were imported from the wild but in the late 1970s, the RIVM started a monkey breeding program to gain more control over the 'quality' of the monkeys being used. In the 1980s, monkey welfare became increasingly important: for example, animal technicians tried to figure out the 'housing preferences' of the monkeys. In this chapter I will show how these developments and others affected the lives of different generations of Polio-monkeys at the RIVM. Researchers at the institute also played a major role in improving the vaccine and the production method, including adaptations to the production method that decreased the number of monkeys being used and eventually led to the switch away from monkey cells to a continuous cell line. This switch was implemented many years after it was technically possible; gaining insight into why this switch was made when it was is therefore an important contribution of this chapter.

Chapter 4 deals with a completely different group of primates: the humans of the Animal Experiments Committee (AEC) tasked with reviewing the (ethical) permissibility of nonhuman animal experiments. Today, the existence of such committees is widely accepted as part of 'good science'. The chapter will show, however, that creating national legislation which required institutes to have their experiments reviewed was met

with a lot of resistance and even deemed 'catastrophic' by some scientists. Animal advocates in turn worried that the legislation would not be strict enough and both groups employed a variety of strategies to influence the politicians that were to create the legislation. The chapter looks beyond the legal aspects to the actual practice of ethically reviewing nonhuman animal experiments in these committees. We will see that the instructions given in the law regarding ethical reviews are contradictory and impossible to translate into practice. I discuss a few specific cases of the RIVM-AEC to offer a better idea of what kind of arguments were entertained in the reviewing process and how these affected the lives of the nonhuman animals that, depending on the review outcome, would or would not be experimented upon.

In Chapters 5 and 6, we move away from primates to focus on mice. We will return to the story of the XPA-mouse in the opening picture as well as other XPA-mice that lived at the RIVM. This story is split into two chapters: the first chapter deals with how and why these mice came to exist, were used, and eventually ceased to exist and the second chapter focuses on the daily lives of these mice and their interactions with humans. Scientists created the XPA-mouse with the aim of replacing 'regular' mice in carcinogenicity testing, hoping that using mice more susceptible to cancer would make it possible to reduce the number of mice needed. The XPA-mice were part of an international program which tested several transgenic mice that could potentially replace regular mice. In the end, the XPA-mice were not the favored candidates for this job and their breeding program ended. As we will see, this was not because another transgenic mouse was created that was more 'perfect' for the job. There were many factors that figured into the decision not to use XPA-mice, including economic and political ones. Through this specific story, the chapters also tell the more general story of the 'transgenic dreams' of the 1980s and 1990 versus the realities which followed afterwards for mice and humans.

These six chapters are followed by a conclusion where I return to the questions posed in the beginning of this introduction. In the conclusion I also reflect on my aim to write multispecies histories and on whether anything can be gleaned from these multispecies histories which serves the desired transition towards using nonanimal alternatives.

The thesis ends with an epilogue in which I share my experiences with using performance to engage with 'the public' about histories of nonhuman animal experimentation and interspecies relations more generally.

A FINAL NOTE ON WORD CHOICE

It is common to use the term animal to denote nonhuman animals. Since I do not want to reproduce a human/animal dichotomy but contribute to its deconstruction, I will use 'nonhuman animals' or sometimes 'other animals'. When I use 'animals', I mean this to include humans as well. I might be sacrificing some legibility here, but I think that it is worth it, especially if doing this challenges readers' conceptions of these terms as well. When it comes to citations, however, I stick to the word choice of whomever I am quoting. In addition to using nonhuman animals, I will occasionally also use 'tested (nonhuman) animals' instead of the more common 'test animals' in order to reflect that these animals were tested upon but cannot be reduced to their usage in experiments or essentialized as inherently being test animals.

A final word choice I made was to use the acronym RIVM throughout the thesis, even

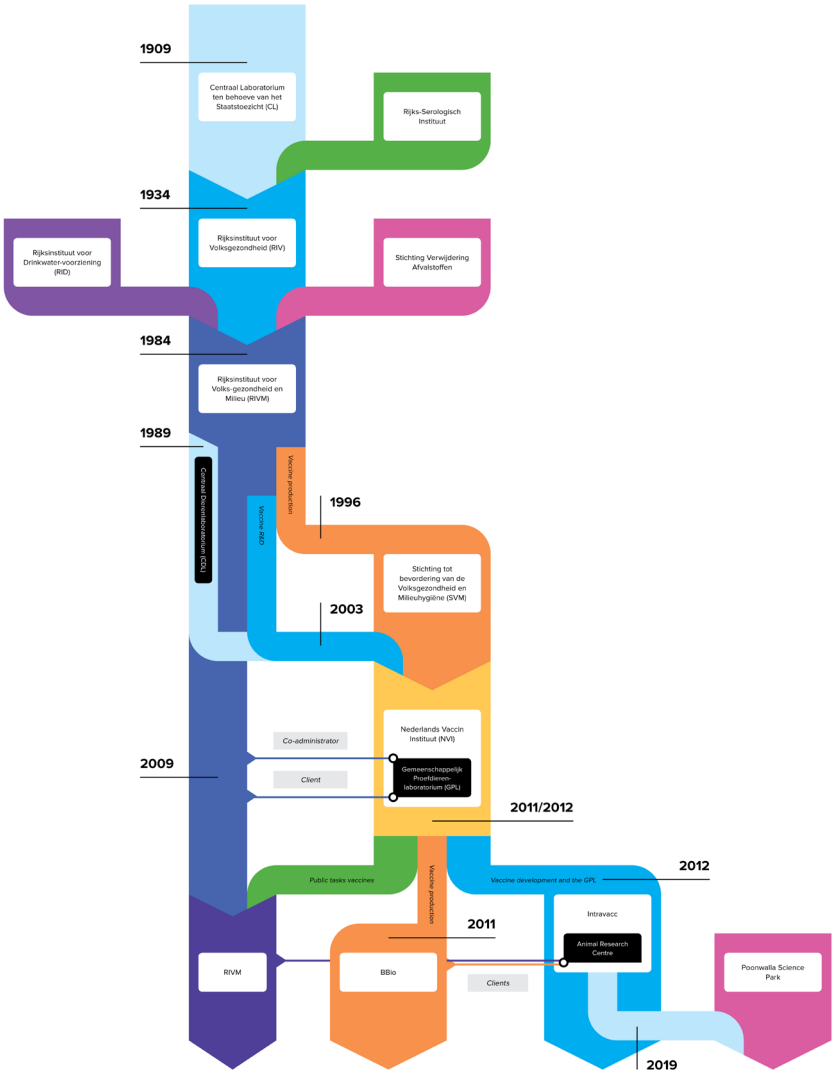

Figure I.2 Schematic Overview RIV(M), SVM, NVI, Intravacc, BBIO

though the institute was called RIV until 1984.[25]

25 In 1984 the RIV merged with two other government institutes which were concerned with drinking water (Rijksinstituut voor Drinkwatervoorziening) and waste products (Stichting Verwijdering Afvalstoffen) and became RIVM. See Henk van Zon. Tachtig jaar RIVM. Van Gorcum, 1990 for a history of the institute until 1990. See figure I.2 for a schematic of how the RIVM developed as an organization.

CHAPTER ONE

Theoretical Framework and Methods

CHAPTER 1: THEORETICAL FRAMEWORK AND METHODS

1.1 INTRODUCTION

In the introduction to this thesis, I stated my aim to write a multispecies history of nonhuman animal testing in the Netherlands that moves beyond anthropocentrism. In order to do this, I have turned to research from a variety of disciplines for developing a theoretical framework for writing multispecies histories. In this chapter, I describe these studies and how they have affected this thesis. Most historical scholarship is not theory-driven and the present work is no different. It is, however, inspired and influenced by theory from several different disciplines, and I find it important that historians make the effort to name their theoretical influences explicitly, as these influences do affect the choices made in selecting research questions and methodologies and therefore the outcomes of the research.[1] As Jorma Kalela states: 'It is the choices historians make that define the parameters of their studies and this gives them a great responsibility. They are, in relation to their own society, guardians of sound knowledge of the past, and in relation to past societies, instrumental in making sure that justice is done [...]'.[2] The aim of this chapter is thus to make clear what my role has been in this research by accounting for the choices I made with regard to my research questions, sources, and how these sources were used. It is not an exhaustive overview of all literature on nonhuman animal testing or even of all literature used in this thesis. The focus, instead, is on literature that affected the choices I made related to methods and research questions.

I will first discuss the *animal turn* in history (1.2). During the last decades, nonhuman animals have received increasing attention in historical scholarship, leading a number of scholars to argue that an 'animal turn' in history has begun.[3] They also note, however, that much work remains to be done, since a radical decentering of the human is not yet commonplace in historical work that focuses on nonhuman animals. To help us move beyond anthropocentrism in historical scholarship, we can turn to other disciplines where useful work has been done in this area. Therefore, following the section on the animal turn I will discuss other work that has been inspirational in writing this thesis, after which I will make explicit how different theoretical approaches influenced the analytical concepts and methods I employed.

I will start with a discussion of (Feminist) Science and Technology Studies and Care

1 Cf. Catherine L. Duxbury, Animal, Gender and Science: Animal Experimentation in Britain, 1947-1965, 2016 http://repository.essex.ac.uk/19887/1/Thesis%20Final.pdf [accessed 24 May 2018]; Hilda Kean, 'Challenges for Historians Writing Animal–Human History: What Is Really Enough?', Anthrozoös, 25.sup1 (2012), s57–72 <https://doi.org/10.2752/175303712X13353430377011>.

2 Cited in Kean, Challenges for Historians, 24.

3 Kean, Challenges for Historians; Harriet Ritvo, 'On the Animal Turn', Daedalus, 136.4 (2007), 118–22; Joshua Specht, '"Animal History after Its Triumph: Unexpected Animals, Evolutionary Approaches, and the Animal Lens"', History Compass, 14.7 (2016), 326–36 <https://doi.org/10.1111/hic3.12322>; Abigail 1972- Woods and others, Animals and the Shaping of Modern Medicine: One Health and Its Histories, Medicine and Biomedical Sciences in Modern History, 1 online resource (xvii, 280 pages) : illustrations vols (Cham: Palgrave Macmillan, 2018) <http://doi.org/10.1007/978-3-319-64337-3> [accessed 23 February 2021].

studies (1.3).[4] Within STS scholarship on nonhuman animal experimentation, useful concepts have been developed to analyze interactions between humans and other animals in the laboratory. These concepts assume more-than-human agency and as such are helpful in showing non-human animals as individuals and subjects. These studies also address the complicated relationship between instrumentalization of, and care for, other animals. This has shown for example that care is material, relational, and performative, plays a crucial role in scientific knowledge production, and that care and instrumentality are not mutually exclusive.[5] The focus on multispecies entanglement can thus be instructive in analyzing micro-level interactions in past practices of nonhuman animal experimentation. It has however also been criticized, most notably by scholars within Critical Animal Studies (CAS) and those working at the boundary between CAS and posthumanism. These scholars argue that more attention should be paid to structural forces that limit the manifestations of non-human agency and condemn all instrumental use of other animals. In the section on CAS, I take a closer look at their position and how it differs from STS (1.4). In the section on posthumanism, I focus on a specific critical posthumanist approach proposed by Hollin et al., in which the authors seek to include structural forces in their analysis by focusing on what is excluded, rather than (only) on interspecies entanglements which have been included (1.5).[6]

Posthumanism aims to decenter the human and provides analytical concepts for rethinking animal experimentation to include more than human agencies and response-abilities, demonstrating how both humans and non-humans are co-constituted in interaction.[7] Posthumanism thus should not be seen as separate or different from STS and CAS, as many scholars within these disciplines take a posthumanist approach to interspecies relations. As we will see in the section on posthumanism, there are many strands of thought within this field; scholars coming from a CAS background generally propose a different understanding of posthumanism than STS scholars. These differences will be fleshed out in the sections to follow. The key take-away is the importance of the macro-level and socio-cultural power relations in the understanding of micro-level interactions in the laboratory. For further cues on how to include macro-level and power relations in my analysis, I turn to *political philosophy* as a final source of insight (1.6). Where history is said to have experienced an animal turn, animal studies

4 For the sake of simplicity, from here on referred to as STS.

5 Gail Davies and others, 'Science, Culture, and Care in Laboratory Animal Research: Interdisciplinary Perspectives on the History and Future of the 3Rs', Science, Technology, & Human Values, 43.4 (2018), 603–21 <https://doi.org/10.1177/0162243918757034>; Tone Druglitrø, '"Skilled Care" and the Making of Good Science', Science, Technology, & Human Values, 43.4 (2018), 649–70 <https://doi.org/10.1177/0162243916688093>; Carrie Friese and Joanna Latimer, 'Entanglements in Health and Well-Being: Working with Model Organisms in Biomedicine and Bioscience', Medical Anthropology Quarterly, 33.1 (2019), 120–37 <https://doi.org/10.1111/maq.12489>.

6 Gregory Hollin and others, '(Dis)Entangling Barad: Materialisms and Ethics', Social Studies of Science, 47.6 (2017), 918–41 <https://doi.org/10.1177/0306312717728344>.

7 Beth Greenhough and Emma Roe, 'Attuning to Laboratory Animals and Telling Stories: Learning Animal Geography Research Skills from Animal Technologists', Environment and Planning D: Society and Space, 37.2 (2019), 367–84 <https://doi.org/10.1177/0263775818807720>; Richard Twine, 'Genomic Natures Read through Posthumanisms', The Sociological Review, 58.1_suppl (2010), 175–95 <https://doi.org/10.1111/j.1467-954X.2010.01917.x>. More generally in posthumanism and animal studies, see Cary Wolfe, 'Human, All Too Human: "Animal Studies" and the Humanities', PMLA, 124.2 (2009), 564–75 and Cary Wolfe, What Is Posthumanism? (Minneapolis, UNITED STATES: University of Minnesota Press, 2009).

is said to have experienced a 'political turn'. Scholars promoting this turn argue that to understand interspecies relations, we need to consider nonhuman animals to be political agents and apply concepts from political philosophy to analyze interspecies relations. After my discussion of these disciplines, I will conclude by explaining how they have affected my research and make explicit how they have affected the choices I made in case studies and research questions (1.7). I will pay special attention to tensions between these approaches in order to make the theoretical positioning of this research as clear as possible. In the final section, I will describe what all this has meant for the use of sources in this thesis (1.8).

1.2 THE 'ANIMAL TURN' IN HISTORY

Nonhuman animals have received increasing attention in historical scholarship during the past decades.[8] According to Joshua Specht, who gives an overview of 'the animal turn' in history, nonhuman animals are no longer the underdog but have become part of mainstream history.[9] However, as I mentioned in the introduction, if we want to write non-anthropocentric history, more is required than simply including other animals as research topics. The animal turn is about more than just 'filling the gaps' of the historical body of research with nonhuman animals.[10] It challenges us to think about what we mean by human and animal, how this has shaped our record keeping and history writing until now, and how we can develop historiographic practices that move beyond anthropocentrism.[11] As we saw in the introduction, according to Anita Guerrini, writing animal histories that radically decenter the human will enable us to, 'deconstruct the animal-human divide and begin to write a new history that can underpin a new ethics for the Anthropocene'.[12] Similarly, Hilda Kean argues that the analysis of this human-animal divide is where historical research can make an important contribution:

> We analyze both broad trends and very specific moments and examples. Such approaches are givens. As cultural historian Joanna Bourke has recently argued, in every period of history and every culture 'commonsensical constructions of "the human" and "the animal" exist, but the distinction is constantly undermined and re-constructed' hence the need for clarity about specific time and place (Bourke 2011, p. 5).13

8 Etienne Benson, 'Animal Writes : Historiography, Disciplinarity, and the Animal Trace', Making Animal Meaning, 2011, 3–16; Erica Fudge, 'A Left-Handed Blow : Writing the History of Animals', in Representing Animals, ed. by Nigel Rothfels (Bloomington: Indiana University Press, 2002), pp. 3–18 <https://strathprints.strath.ac.uk/29540/> [accessed 25 February 2021]; Kean, Challenges for Historians; Ritvo, 'On the Animal Turn'; Specht, Animal History.

9 Specht, Animal History, 326 & 331.

10 Kean, Challenges for Historians; Specht, Animal History.

11 The role of the historian in writing history and the use of sources are elaborated on in section 8.

12 Anita Guerrini, 'Deep History, Evolutionary History, and Animals in the Anthropocene', in Animal Ethics in the Age of Humans: Blurring Boundaries in Human-Animal Relationships, ed. by Bernice Bovenkerk and Jozef Keulartz, The International Library of Environmental, Agricultural and Food Ethics (Cham: Springer International Publishing, 2016), pp. 25–37 <https://doi.org/10.1007/978-3-319-44206-8_2>, 26.

13 Kean, Challenges for Historians, 59.

Looking at historical writing about nonhuman animals, we can see that this radical decentering of the human and deconstruction of the human/animal divide is not yet commonplace in animal history writing. Specht has identified several trends in animal history in the last decades, which he calls 'the animal lens', 'unexpected animals', and 'evolutionary history'.[14] The animal lens approach is widespread and involves looking at historical events which have already been studied from a human perspective through the eyes of nonhuman animals, focusing on human-animal relations. Animals have been at the center of human societies throughout history but are often missing from historical records. Therefore, employing the animal lens can reveal new perspectives and understandings as well as challenge us to think about who the 'we' of history is. While these new perspectives are valuable for a richer understanding of history, Specht also warns of the risks involved in this approach. Animal lens approaches tend to instrumentalize animals; they only matter because they can elucidate human history, making the animal lens more an 'animal mirror'.[15] If we want to truly decenter the human, we should treat nonhuman animals as subjects with their own histories, that may or may not involve humans.

'Unexpected animals' and 'evolutionary history' are more recent trends, the latter of which is especially significant for this thesis since it focuses on 'anthropogenic evolution': how nonhuman animal bodies have been shaped by humans and the role of economic and technological change in this process.[16] The study of experimental nonhuman animals could fit well with the 'evolutionary history' approach. However, the way these histories are often written tends to lose sight of nonhuman animals as individuals and reduce them to their genes. The useful takeaway from this trend is instead the relevance of structural forces that constrain the lives of nonhuman animals, as long as we keep in mind that in the end it is individual nonhuman animals that are feeling the effects of these structural forces, and their histories are worth telling.

Specht lastly addresses the issue of agency and argues that the current focus on the agency of nonhuman animals (and other marginalized groups) is counterproductive:

> The emphasis on individual autonomy—human or otherwise—provides voice and power to neglected groups, but risks obscuring the structural forces that constrain their actions and explain different actors' historical marginality in the first place. An investment in proving animal agency can actually have the effect of minimizing the profound ways that humans have circumscribed and dominated animal life.[17]

Summary & Takeaways

Nonhuman animals have become part of historical research, but historians are still searching for ways to write history that radically decenters the human. To do justice to other animals, historians need to do more than simply 'fill in the gaps'; we must make sure not to instrumentalize or deindividualize nonhuman animals. To understand the lives of animals in the past and their often-marginalized positions, we need to account

14 Specht, Animal History.

15 Specht, Animal History, 326-328.

16 By 'unexpected animals' Specht means nonhuman animals that have traditionally not been at the center of human society, for example roadkill and fire ants. Specht, Animal History, 329-330.

17 Ibidem, 332.

for the structural forces that have affected their lives. By doing this, we can make important contributions both to the existing historical body of knowledge and to moving towards non-anthropocentric ethical practices in the present and future.

1.3 (FEMINIST) SCIENCE & TECHNOLOGY STUDIES (STS) & CARE STUDIES

STS studies on nonhuman animal experimentation focuses strongly on care and multispecies entanglement, foregrounding both human and nonhuman animals as embodied agents. This body of work has shown that nonhuman animals are an integral and active part of scientific knowledge production and that practices of nonhuman animal experimentation are not standardizable.[18] Tacit knowledge and cross-species attunement play important roles; both human and nonhuman bodies are changed in their interaction.[19] Building on the influential work of Donna Haraway, humans and other animals are seen in this literature as 'response-able'—a capacity which is by definition relational, always implicating multiple beings becoming together intra-actively.[20] STS therefore focuses on relations between humans and nonhumans. STS scholars often use ethnographic methods, providing rich descriptions at the level of the laboratory, taking nonhuman animals seriously as embodied subjects, and as such providing valuable contributions for historical works that wish to decenter the human. Below, I discuss three important concepts from STS that I will use in this thesis: response-ability, (culture of) care, and attunement. Subsequently, I will discuss the criticisms of these approaches as well as the feminist ethics-of-care approach that positions itself as fundamentally different from STS approaches, but also centers around care.

Response-ability

STS research on nonhuman animal experimentation builds on feminist studies, most notably the works of Donna Haraway (whose work is sometimes also referred to as feminist science studies). Kheel writes about how feminist studies aims to challenge dualisms such as nature/culture and human/animal.[21] Dualistic thinking has a long

18 Gail Davies, 'Mobilizing Experimental Life: Spaces of Becoming with Mutant Mice', Theory, Culture & Society, 30.7–8 (2013), 129–53 <https://doi.org/10.1177/0263276413496285>; Druglitrø, Skilled Care.

19 Beth Greenhough and Emma Roe, 'Attuning to Laboratory Animals and Telling Stories: Learning Animal Geography Research Skills from Animal Technologists', Environment and Planning D: Society and Space, 37.2 (2019), 367–84 <https://doi.org/10.1177/0263775818807720>; Vinciane Despret, 'The Body We Care for: Figures of Anthropo-Zoo-Genesis', Body & Society, 10.2–3 (2004), 111–34 <https://doi.org/10.1177/1357034X04042938>.

20 Donna J. Haraway, When Species Meet (U of Minnesota Press, 2013). According to the New Materialism almanac, 'intra-action is a Baradian term used to replace 'interaction,' which necessitates pre-established bodies that then participate in action with each other. Intra-action understands agency as not an inherent property of an individual or human to be exercised, but as a dynamism of forces (Barad, 2007, p. 141) in which all designated 'things' are constantly exchanging and diffracting, influencing and working inseparably. Intra-action also acknowledges the impossibility of an absolute separation or classically understood objectivity, in which an apparatus (a technology or medium used to measure a property) or a person using an apparatus are not considered to be part of the process that allows for specifically located 'outcomes' or measurement.' Whitney Stark, 'Intra-action' (2016) <https://newmaterialism.eu/almanac/i/intra-action.html> [accessed 25 February 2021].

21 Marti Kheel, 'The Liberation of Nature: A Circular Affair', Environmental Ethics, 1985, 135–49 <https://doi.

history and is at the core of many forms of exploitation. In contrast, feminist thinking proposes holistic, relational thinking which provides space for both emotionality and rationality rather than seeing them as mutually exclusive.[22]

Haraway also addresses dualisms in her work, proposing for example *natureculture* instead of nature/culture as a dichotomy.[23] Her reading of responsibility is crucial for how laboratory interactions, or rather 'intra-actions', between humans and other animals are viewed. According to Haraway, both humans and other animals are response-able and therefore share responsibility. Thus, in this view, nonhuman animals are active participants in the lab. Haraway goes as far as to describe tested animals as 'workers' and animal experimentation as co-laboring. Writing about 'shared conditions of work', she describes:

> Human beings are not uniquely obligated to and gifted with the responsibility; animals as workers in labs, animals in all their worlds, are response-able in the same sense as people are; that is, responsibility is a relationship crafted in intra-action through which entities, subjects, and objects, come into being.[24]

Therefore, Haraway argues, we should not study humans and other animals as fully separate individuals that possess responsibility, but rather we should analyze how both are co-constituted. Closely related to the concept of response-ability, is the concept of attunement, which can be seen as a specific type of response to one another.

Attunement

> This is, in my opinion, the most interesting characteristic of the practices that may be defined as practices of domestication, the practices that allow themselves to be pervaded by humans: they are practices that create and transform through the miracle of attunement. This miracle of attunement, be it between Hans and his questioners, between horses and their riders, or between rats and their student-experimenters, radically changes the question we may address to the body.[25]

STS scholars have drawn on the work of Vinciane Despret to describe how humans and nonhumans learn to attune to one another in the context of the animal laboratory. For Despret, attunement is about affected and affecting bodies, about emotions. Attune-

org/10.5840/enviroethics19857223>.

22 On rationality and emotion, see also: Carol L. Glasser, 'Rational Emotions: Animal Rights Theory, Feminist Critiques and Activist Insight', in The Psychology of the Human-Animal Bond: A Resource for Clinicians and Researchers, ed. by Christopher Blazina, Güler Boyraz, and David Shen-Miller (New York, NY: Springer, 2011), pp. 307–19 <https://doi.org/10.1007/978-1-4419-9761-6_18>.

23 Donna Jeanne Haraway, The Companion Species Manifesto: Dogs, People, and Significant Otherness, Paradigm ; 8 (Chicago: Prickly Paradigm Press, 2003) <http://catdir.loc.gov/catdir/description/uchi052/2002115995.html> [accessed 25 February 2021].

24 Haraway, When Species Meet, 71.

25 Vinciane Despret, 'The Body We Care for: Figures of Anthropo-Zoo-Genesis', Body & Society, 10.2–3 (2004), 111–34 <https://doi.org/10.1177/1357034X04042938>, 125.

ment is different from empathy, though the ability to empathize is required to attune the body. Attunement is not learning 'what it is like to be someone, but what it is to be with some-one', a responding to one another, a relational co-constitution as described above by Haraway.[26]

Empathy and attunement are not understood as unscientific, but rather as scientific tools instrumental in producing better quality research outcomes.[27] Greenhough and Roe studied the attunement of Animal Technicians (ATs) to laboratory animals, finding that '[...] attunement is a resource drawn on both instrumentally (as part of fulfilling requirements to monitor and promote good animal welfare) and affectively (as a resource to develop the capacity for animal care; seen as central to being a good AT)'.[28] Although these authors focused on attunement from the perspective of ATs, attunement is a two-way-process that happens within the relation between the AT and the lab animal. Having observed ATs at work, they argue that acts of 'skillful seeing' take place in the laboratory in which '[...] animals and humans attune to each other through the ways in which humans manipulated, handled, caressed, fed and encouraged the animals they care-work with.'[29] Through bodily attunement, ATs learn not only to skillfully see general murine facial expression, but also become sensitized to the varying characteristics and sensibilities of different strains of mice (something we will also see in the chapters about the XPA-mice).

Within the laboratory, there are both constraining and enabling elements when it comes to attunement between ATs and lab animals.[30] For example, cages in animal houses are set up in such a way that visual inspection of nonhuman animals by ATs can be easily performed. On the other hand, structural constraints severely limit the response-abilities of lab animals as well as ATs.[31] According to Greenhough & Roe, attunement should not be seen as separate from the overarching structure within which it takes place: 'If we learn anything from the ATs here, it is that the infrastructure imposes an inability to escape animal exploitation, and AT attunement to animals is part and parcel of that'.[32] While attunement could thus be seen as facilitating nonhuman animal exploitation, they argue that the stories of ATs and their becoming with lab animals might also be part of a strategy to renegotiate human animal relations, as their stories '[...] challenge and resist the animals' reduction to passive objects exploited for purely instrumental ends'.[33]

(Culture of) care

The historical works of Robert Kirk and Tone Druglitrø have shown how care for laboratory animals became professionalized in the 1950s in the UK and Norway, when it

26 Despret, The Body We Care for; Vinciane Despret, 'Responding Bodies and Partial Affinities in Human–Animal Worlds', Theory, Culture & Society, 30.7–8 (2013), 51–76 <https://doi.org/10.1177/0263276413496852>.

27 Despret, Responding Bodies; Greenhough & Roe, Attuning to laboratory animals.

28 Greenhough & Roe, Attuning to laboratory animals, 373.

29 Ibidem, 372.

30 Ibidem.

31 Anne van Veen, 'The Life of an XPA-Mouse. A Posthumanist Approach to Becoming with Humans in Laboratory and Law', TRACE ∴ Journal for Human-Animal Studies, 6.1 (2020), 26–51 <https://doi.org/10.23984/fjhas.78050>.

32 Greenhough & Roe, Attuning to laboratory animals, 374.

33 Ibidem, 369.

was recognized that animal welfare had an effect on experimental results.[34] Care in the laboratory was in that way instrumental and an integral part of scientific knowledge production. The work within care studies argues, however, that care in the laboratory is complex and multifaceted and about more than just instrumentality. According to Davies et al. 'Animal use and animal care are not separated but connected through capacities to recognize and respond to the suffering of another; what is inadequate in this conceptual formulation are the administrative techniques like cost (or more usually harm)/benefit analysis in accounting for this ethical relation.'[35] Caring in the laboratory involves affection, physical skills, and ethical decision making.[36] Ethnographic research by Greenhough and Roe has shown how a culture-of-care is created at animal research institutes, in which animal technicians often go beyond what is legally required in their caring practices.[37] The fact that care moves beyond instrumentality and involves affection on the part of caregivers should not be understood to mean that this care is 'innocent' or that human-lab animal relations should be seen as equal just because both are response-able. As Friese & Latimer explain: 'STS scholarship has argued that care is not innocent and cannot be valorized as a way out of unequal relations; care can just as often also cement hierarchies (Giraud and Hollin 2016; Martin et al. 2015, Murphy 2015)'.[38]

The relationship between care and domination is explored further by Holmberg in her article 'Mortal Love', in which she attempts to understand the dialectic between care, on the one hand, and instrumentality and exploitation on the other.[39] She finds that laboratory animals can be both lovable and killable in relation to animal technicians and scientists. When nonhuman animals are loved, effort is required to make them killable, and the killing is made more acceptable (to the ones performing the killing) by focusing on 'killing with care'. In conclusion, Holmberg argues that 'emotions of love and friendship are not mere justifications for the harm and killing performed, but rather intrinsic dimensions of the embodied animaling of experimental human–animal relations.'[40] While for Holmberg this justifies a focus on the interactions in the laboratory, others have argued that to understand the meaning of care and domination for the lives of lab animals, we need to look closer at systems of oppression rather than at day-to-day interactions.

34 Druglitrø, Skilled Care; Robert G. W. Kirk, 'Care in the Cage: Materializing Moral Economies of Animal Care in the Biomedical Sciences, c.1945-', in Animal Housing and Human-Animal Relations: Politics, Practices and Infrastructures, ed. by Kristian Bjørkdahl and Tone Druglitrø, Wellcome Trust–Funded Monographs and Book Chapters (Oxon (UK): Routledge, 2018) <http://www.ncbi.nlm.nih.gov/books/NBK539323/> [accessed 23 February 2021].

35 Davies et al., Science, Culture and Care, 605.

36 Ibidem; Druglitrø, Skilled Care.

37 Beth Greenhough and Emma Roe, 'Exploring the Role of Animal Technologists in Implementing the 3Rs: An Ethnographic Investigation of the UK University Sector', Science, Technology, & Human Values, 43.4 (2018), 694–722 <https://doi.org/10.1177/0162243917718066>.

38 Carrie Friese and Joanna Latimer, 'Entanglements in Health and Well-Being: Working with Model Organisms in Biomedicine and Bioscience', Medical Anthropology Quarterly, 33.1 (2019), 120–37 <https://doi.org/10.1111/maq.12489>, 123.

39 Tora Holmberg, 'Mortal Love: Care Practices in Animal Experimentation', Feminist Theory, 12.2 (2011), 147–63.

40 Ibidem, 161.

Critique and alternative readings of care

There has been critique of STS's focus on care and entanglement, both from scholars in critical animal studies (CAS) and critical posthumanism. According to these scholars, a lens that too narrowly focuses on multispecies entanglement lacks attention to power relations and to how care and welfare are used to facilitate or legitimize continued oppressive relations such as nonhuman animal experimentation.[41] For example, Haraway is often criticized for arguing that nonhuman animal experimentation should be done 'responsibly', rather than challenging the underlying power inequality.[42] While in care studies a constraining wider context is often acknowledged, it generally is not given much attention in analyzing practices, since the focus is on cross-species entanglement. Adams and Donovan propose a feminist ethics-of-care that is fundamentally different from work based on Haraway's ideas of responsible nonhuman animal experimentation. They argue that an ethics-of-care approach should look not only at individual suffering but also at 'the political and economic systems that are causing the suffering' and that caring for experimental animals means dismantling these oppressive systems, not operating 'caringly' within them.[43] So, rather than a renegotiation within the laboratory context—where nonhuman animals currently have hardly any room to negotiate since their response-abilities are severely limited by interspecies power relations—the authors argue that the focus should be on how to change these underlying inequalities that make the practice of (non-consensual) nonhuman animal experimentation possible.[44] This criticism is shared by scholars within critical posthumanism and critical animal studies and will be explored further in my discussion of these fields in later sections.

Summary & Takeaways

STS studies focusing on care have provided valuable concepts and insights for analyzing historical practices of animal experimentation. They point out the importance of looking at the day-to-day level of interaction in the laboratory where the response-abilities of individuals from multiple species manifest themselves and where human and nonhuman animal bodies are co-constituted. Critiques of these studies have pointed out some important limitations. These critiques are in line with Specht's warning that we should not focus too much on individual agency and pay close attention to structural forces. This issue will be discussed further when I look at (critical) posthumanism and critical animal studies (CAS), where similar debates take place.

41 Greenhough & Roe, Attuning to laboratory animals; Eva Giraud and Gregory Hollin, 'Care, Laboratory Beagles and Affective Utopia', Theory, Culture & Society, 33.4 (2016), 27–49 <https://doi.org/10.1177/0263276415619685>; Lonneke Poort, Tora Holmberg, and Malin Ideland, 'Bringing in the Controversy: Re-Politicizing the de-Politicized Strategy of Ethics Committees', Life Sciences, Society and Policy, 9.1 (2013), 11 <https://doi.org/10.1186/2195-7819-9-11>. Richard. Twine, Animals as Biotechnology: Ethics, Sustainability and Critical Animal Studies, Science in Society Series, 1 online resource (vi, 222 pages) vols (London ; Earthscan, 2010) <http://public.eblib.com/choice/publicfullrecord.aspx?p=585513> [accessed 25 February 2021].

42 Josephine 1941- Donovan and Carol J. Adams, The Feminist Care Tradition in Animal Ethics: A Reader (New York: Columbia University Press, 2007).

43 Ibidem, 3.

44 See also Van Veen, The life of an XPA-mouse.

1.4 (CRITICAL) ANIMAL STUDIES

Critical Animal Studies (CAS) developed in the beginning of the 21st century in response to Animal Studies ((AS), also referred to as Mainstream Animal Studies (MAS)) out of disappointment with MAS scholarship and has been growing rapidly since then.[45] Taylor and Twine mention several characteristics of CAS that set it apart from other approaches concerned with ´the question of the animal´.[46] CAS has a very specific focus on not just the question of the animal, but also the condition of the animal, which logically follows from CAS's emergence out of a nexus of science, politics, and activism. Following from this, CAS is explicitly political, taking a normative stance against animal exploitation and 'the anthropocentric status quo in human-animal relations, as demonstrated in current mainstream practices and social norms.'[47] While the main concern of CAS is the condition of the animal, it approaches this from an intersectional perspective and is strongly influenced by activist/scholars from feminist and critical race scholarship, sharing with them a critique of the 'academic-industrial complex' and oppressive knowledge structures.[48] Another important characteristic of CAS is a focus on political economy and a critical analysis of how capitalism affects nonhuman animals.[49] According to Twine the concept of the 'animal-industrial complex', a term coined by Barbara Noske in 1989, can be useful in analyzing the role of political economy in shaping human-animal relations from an intersectional and interdisciplinary perspective.[50] He defines A-IC as:

> […] a partly opaque and multiple set of networks and relationships between the corporate (agricultural) sector, governments, and public and private science. With economic, cultural, social, and affective dimensions, it encompasses an extensive range of practices, technologies, images, identities, and markets.[51]

Mapping out these networks and relationships through specific case-studies (e.g., of specific companies) can contribute to making the A-IC visible and giving insight into the specific ways in which these networks and relations affect human as well as non-

45 Nik Taylor and Richard Twine, The Rise of Critical Animal Studies: From the Margins to the Centre (Routledge, 2014); Helena Pedersen, 'Release the Moths: Critical Animal Studies and the Posthumanist Impulse', Culture, Theory and Critique, 52.1 (2011), 65–81 <https://doi.org/10.1080/14735784.2011.621663>.

46 Taylor & Twine, The Rise, 2.

47 Ibidem.

48 Jessica Groling, 'Studying Perpetrators of Socially-Sanctioned Violence against Animals through the I/Eye of the CAS Scholar', in Nik Taylor and Richard Twine, The Rise of Critical Animal Studies: From the Margins to the Centre (Routledge, 2014), 88–110; Anthony J. Nocella and others, 'INTRODUCTION: The Emergence of Critical Animal Studies: The Rise of Intersectional Animal Liberation' in Nocella, Anthony J. John Sorenson, Kim Socha, and Atsuko Matsuoka, eds., Defining Critical Animal Studies: An Intersectional Social Justice Approach for Liberation, New edition (New York: Peter Lang Inc., International Academic Publishers, 2013), xix–xxxvi

49 Steve Best, The Rise (and Fall) of Critical Animal Studies (2020). Available online at https://www.researchgate.net/publication/341358498_The_Rise_and_Fall_of_Critical_Animal_Studies_1.

50 Richard Twine, 'Revealing the 'animal-Industrial Complex—A Concept and Method for Critical Animal Studies', Journal for Critical Animal Studies, 10.1 (2012), 12–39.

51 Ibidem, 23.

human animals.[52] Twine gives the example of livestock genetics companies (LCGs) as a case study, showing that these companies operate in a network including academia and government, together forming a 'biopolitical coalition disciplining the animal body and inciting new strategies of capital accumulation from farmed animals'.[53] While the focus is often on animal agriculture, the A-IC includes animal experimentation and an analysis of how the latter relates to the former, as well as to the 'academic-industrial complex' mentioned before.[54]

Animal experimentation is an unacceptable aspect of academic research from a CAS perspective, in which it is seen as a form of 'socially-sanctioned violence against animals'.[55] Groling argues that while ethnographic research into animal experimentation has yielded valuable insights into the socialization processes at work within the animal laboratory and the psychological mechanisms employed by laboratory workers to deal with the demands of their job, this type of research is also problematic since researchers participate in oppressive practices.[56] She emphasizes the importance of looking beyond individual psychology and uncovering speciesist structures through a situationist focus which:

> [...] would enable us to outline how the defensive devices and ideologies that offer justifications and rationalizations for experimentation on live animals are embedded in the collective consciousness, cultural tools, regulatory practices and infrastructure of the institution in question and give rise to interactional dynamics that can account for particular mediations of meaning and identity.[57]

This position on nonhuman animal experimentation is fundamentally different from that of Haraway and the other scholars building on her work, discussed in the previous section. CAS scholars logically do not take issue with the recognition of more-than-human agencies and attempts to move beyond anthropocentrism that are characteristic of posthumanist (science) studies, but they are critical of the way posthumanism is often practiced.[58] One important criticism that has been leveraged is that posthumanism has become depoliticized, rethinking but not remaking human-animal relations.[59] For some CAS scholars, this means that CAS should abandon posthumanism altogether and instead further develop humanist critical theory. Weisberg states that critical animal studies scholars should distance themselves from posthumanism because while

52 Human animals are included, since from an intersectional perspective their plight is also part of the analysis.

53 Ibidem, 26.

54 Twine argues the importance of looking for overlaps between different complexes and not setting fixed boundaries in defining the A-IC.

55 Groling, Studying Perpetrators.

56 Ibidem.

57 Ibidem, 93.

58 I speak of posthumanist science studies, since the critique of CAS pertains to both posthumanism-inspired science studies (such as described in the previous section) and posthumanism in general.

59 Eva Giraud, '"Beasts of Burden": Productive Tensions between Haraway and Radical Animal Rights Activism', Culture, Theory and Critique, 54.1 (2013), 102–20 <https://doi.org/10.1080/14735784.2013.769724>; Pedersen, Release the Moths; Zipporah Weisberg, 'The Trouble with Posthumanism: Bacteria Are People Too', Critical Animal Studies: Thinking the Unthinkable, 2014, 93–116.

it has its merits in challenging human exceptionalism, it also celebrates hybridity and boundary dissolution without regard for the practical consequences of these for actual living beings. An example is the case of Haraway's celebration of the 'OncoMouse' as a hybrid that challenges a human/animal boundary, but without acknowledgement of the suffering and continued human domination individual OncoMice are subjected to.[60] In these ways, posthumanism poses the risk of moving CAS away from politics and ethics. Pedersen explains:

> From a critical animal studies perspective, tendencies towards subject boundary dissolution are never symmetrical and therefore cannot be innocent. Surely most nonhuman animals have never expressed any desire whatsoever to 'co-emerge' with the species that, to them, above all means violence, horror, and death? Theorizing boundary-dissolution is relatively unproblematic for those who never need to experience oppression: those to whom life is a constant struggle with suffering imposed by others, are likely to be more keen on protecting their subject boundaries from uninvited intervention.[61]

According to Pedersen, posthumanism as a theoretical approach does not automatically lead to a commitment to improving the lives of nonhuman animals and, as we will soon see, even entails the risk of legitimizing oppressive structures. This leads her to ask:

> So, what does posthumanism do for the situation of "real" animals? Exactly how does it intervene in the lives of its innumerable commodified hybrid companion species such as OncoMice, Enviropigs, the broiler chicken breed Cobb 500? (Or even its ostensibly more mundane affiliates, such as the ordinary dairy cow?).[62]

Despite this critical stance, Pedersen and many other CAS scholars do see potential for fruitful cross-pollination between posthumanism and CAS. Both Giraud and Pederson bring CAS and the work of Haraway in conversation with each other to find 'productive tensions' between the two as well as to point out why Haraway's criticism on CAS (discussed below) is, according to them, unjustified. The critical posthumanist approach developed by Giraud (based on bringing together CAS, posthumanism, and ecofeminism) is discussed in the next section on posthumanism. In this section we now take a closer look at the position of CAS scholars vis-à-vis the work of Haraway. Since Haraway's work has been so influential in the study of human-animal relations and (posthumanist) STS approaches to animal experimentation, it is worth diving deeper into the friction between Haraway and CAS to flesh out exactly wherein the differences and similarities lie and what can be taken away from this for researching past practices of animal experimentation.

60 Weisberg, The Trouble with Poshumanism.

61 Pedersen, Release the Moths, 72.

62 Ibidem, 74.

CAS, Haraway, and anthropocentrism

Within CAS, scientific and activist practices go hand-in-hand, with veganism being the practical expression of concern for the condition of the animal, a position often criticized by non-CAS scholars. Haraway has criticized CAS for being dogmatic and anthropocentric because of its focus on the 'humanist' concept of rights and its veganist position.[63] According to Giraud and Pederson, however, veganism should not be seen as a universal dogma but as a praxis: 'By framing veganism as a form of affirmative biopolitics, I suggest that it has the capacity to not only challenge the cultural positioning of animals as exploitable but to unsettle the epistemological categories that legitimize this exploitation'.[64] In turn, from a CAS perspective, Haraway's work is anthropocentric. CAS aligns with Haraway in critiquing human supremacism and the consequences thereof for nonhuman animals, and both are critical of the use of animals in biopolitics. However, Haraway critiques the way nonhuman animals are used in contexts where power relations are asymmetrical, but does not critique these contexts themselves (e.g., she is not opposed to contexts in which nonhuman animals are experimented upon or used for food).[65] Haraway argues that killing nonhuman animals should not be condemned, but that the mantra should be 'thou shalt not make killable'.[66] By arguing however that, for example, it is justifiable (though not innocent) to experiment on nonhuman animals as long as this is done responsibly, nonhuman animals become categorized as killable. Giraud argues:

> Turning this principle [of thou shalt not make killable] against When Species Meet reveals how Haraway's work perpetuates the categorisation of certain animals as 'killable' in a way that secures the structures of biocapital, even as she criticises the excesses of this system. This approach also demonstrates latent anthropocentrism within her work, with her defense of these practices involving labelling any critiques of her case studies as themselves reliant on conceptions of 'inviolable animal rights' (2008: 87), which are grounded in anthropocentric notions of what 'rights' are [...].[67]

Duxbury responds to Haraway's writings on animal experimentations in When Species Meet (including her discussion of response-ability quoted in the previous section) and argues against her separation of instrumentality from oppression: 'Haraway then, reduces the animal, and human to instrumental relations. Yes, mutual and entangled ones, but the key is to recognize that ultimately instrumentalism is domination, hierarchy, and control over others'.[68] According to Pedersen, by 'making lab animals killable', Haraway reinscribes rather than disturbs species boundaries and anthropocentric cultural structures.[69] Continued arguments over who is most anthropocentric are, how-

63 Giraud, Beasts of Burden.

64 Eva Giraud, 'Veganism as Affirmative Biopolitics: Moving Towards a Posthumanist Ethics?', PhaenEx, 8.2 (2013), 47–79 <https://doi.org/10.22329/p.v8i2.4087>, 52; Pedersen, Release the Moths.

65 Giraud, Beasts of Burden; Giraud, Veganism as Affirmative Biopolitics.

66 Haraway, When Species Meet, 105-106.

67 Giraud, Beasts of Burden, 104.

68 Duxbury, Animal, Gender and Science, 60.

69 Pedersen, Release the Moths, 72-76.

ever, also not going to help nonhuman animals. Giraud therefore suggests exploring whether the shared critique of biocapital can be enacted in practice without humanist projections or naturalizing asymmetrical human-animal relations. Activists' praxes, she argues, have the capacity to unsettle the positioning of animals as biocapital more successfully than Haraway's approach. Following Wolfe, she argues that '[…] veganism does not have to be grounded in humanist values, but can function as an affirmative biopolitics that challenges the biopolitical *dispositifs* which render animals exploitable'.[70] An approach that focuses on biopolitics allows for an analysis as well as a challenging of specific cultural and political mechanisms that function to exploit both nonhumans and humans. This brings space for intersectionality and activism whilst not relying on humanist concepts, thereby having the potential to bridge the differences between CAS and posthumanism.[71] Pedersen also sees the value of posthumanist concepts for CAS, proposing a 'cross-infection' between CAS and posthumanism to further decenter the human and challenge a human/animal dichotomy both symbolically and materially by infecting '[...] critical animal studies with some healthy impurity, indeterminacy, and 'surprise', and to root posthumanism in (un)firm political soil with consistent and committed critical attention towards any oppressive institutions, arrangements, and practices that regulate and exploit the life conditions of humans and nonhumans alike'.[72]

In the next section, we will take a closer look at the critical posthumanist approach proposed by Giraud and others following from these productive tensions between CAS and Haraway.

Summary & Takeaways

CAS is characterized by an interdisciplinary and intersectional approach to the study of the question *and* condition of the animal. It is set apart from other disciplines studying nonhuman animals by having emerged from and staying committed to a combination of activism, politics, and science and by taking an explicit stance against oppression of

70 Giraud, Veganism as Affirmative Biopolitics, 51. The term dispositif (also apparatus) is used here following Foucault, who first defined it in an interview as: 'What I'm trying to pick out with this term is, firstly, a thoroughly heterogenous ensemble consisting of discourses, institutions, architectural forms, regulatory decisions, laws, administrative measures, scientific statements, philosophical, moral and philanthropic propositions–in short, the said as much as the unsaid. Such are the elements of the apparatus. The apparatus itself is the system of relations that can be established between these elements.

Secondly, what I am trying to identify in this apparatus is precisely the nature of the connection that can exist between these heterogenous elements. Thus, a particular discourse can figure at one time as the programme of an institution, and at another it can function as a means of justifying or masking a practice which itself remains silent, or as a secondary re-interpretation of this practice, opening out for it a new field of rationality. In short, between these elements, whether discursive or non-discursive, there is a sort of interplay of shifts of position and modifications of function which can also vary very widely. Thirdly, I understand by the term "apparatus" a sort of–shall we say–formation which has as its major function at a given historical moment that of responding to an *urgent need*. The apparatus thus has a dominant strategic function. This may have been, for example, the assimilation of a floating population found to be burdensome for an essentially mercantilist economy: there was a strategic imperative acting here as the matrix for an apparatus which gradually undertook the control or subjection of madness, sexual illness and neurosis.' "The Confession of the Flesh" (1977) interview. In *Power/Knowledge Selected Interviews and Other Writings* (ed. Colin Gordon), 1980: pp. 194-228.

71 Giraud, Veganism as Affirmative Biopolitics.

72 Pedersen, Release the Moths, 78.

animals (both nonhuman and human). In the search for ways to end animal oppression, an analysis of the political economy of human-animal relations and a critique of capitalism is deemed crucial. This stance means that CAS has a complicated position vis-à-vis academia, on the one hand working within it and on the other hand critiquing oppressive knowledge structures, academia's complicity in the 'animal-industrial complex', and, of course, scientific research using nonhuman animals. Many CAS scholars try to find the 'productive edges' with other disciplines such as posthumanism and STS to achieve some cross-pollination and enrich CAS with insightful theories and concepts from other disciplines, as well as to promote the more activist and political stance of CAS among other disciplines.

1.5 (CRITICAL) POSTHUMANISM

Posthumanism is not a single school of thought but rather a constellation of different approaches that have in common that they aim to rethink the human.[73] Richard Twine distinguishes three types of posthumanism (which in turn have different strands within them): antihumanism, transhumanism, and critical posthumanism. It is the critical posthumanist strands that I am most interested in, since they are concerned with a decentering of the human and moving beyond anthropocentrism.[74] As we saw in the previous section, exactly what it means to move beyond anthropocentrism is not always agreed upon. Twine observes a gap between two different takes on the matter:

> There is a disconnect between some critical posthumanist writers, largely to be found within science studies, and the substantial body of work of those writing in animal studies and environmental ethics who are doing significant critical posthumanism. The gap is not total but revolves around different uses of the word anthropocentrism which may be used either in a theoretical ontological sense and/or a more political sense related to critiques of human supremacism. I want to argue that critical posthumanism is at its most coherent and incisive when it builds upon both these uses [...].[75]

Twine's take on critical posthumanism therefore concurs with the works of Giraud and Pedersen discussed earlier in that he sees it necessary to challenge anthropocentrism both on the level of theory and at the level of practice.

Cary Wolfe emphasizes that posthumanism should not only address human privilege, but also the human as knower. It entails more than just making nonhuman animals the subject of research, it requires methodological and theoretical approaches that question the concept of species and the human as 'subjective knower' (Wolfe, 2009).[76] Posthumanist approaches to the study of nonhuman animals are employed in many different disciplines and Wolfe argues that posthumanism cannot be practiced fully when it

73 Twine, Genomic natures, 175.

74 This is in contrast to transhumanism, which 'may be briefly defined as the belief that the human race should be 'enhanced' using technological means'. Twine, Genomic natures, 176.

75 Ibidem, 184.

76 Wolfe, What is Posthumanism.

does not affect the methods and concepts of a scholar's 'home discipline'. In this regard he speaks of 'external' and 'internal' posthumanism and argues that both are necessary:

> So even though your external disciplinarity is posthumanist in taking seriously the existence and ethical stakes of nonhuman beings (in that sense, it questions anthropocentrism), your internal disciplinarity may remain humanist to the core. (Indeed, such is the standard charge leveled against the animal rights philosophy of Singer and Regan: that it tacitly extends a model of human subjectivity to animals, who possess our kind of personhood in diminished form).[77]

I will now discuss two specific critical posthumanist studies that are especially relevant to this thesis in that they have provided insight into how animal experimentation can be analyzed from a critical posthumanist perspective, moving beyond studies of entanglement to also include an analysis of constraining structures. The first article I will discuss is 'Animal Performances' by Birke et al. and the second is '(Dis)entangling Barad: Materialism & Ethics' by Hollin et al..[78] Both are based on the posthumanist performative approach developed by Karen Barad, which has had significant influence across a variety of disciplines.[79] Barad developed a performative, posthumanist onto-epistemo-ethics, combining insights from quantum mechanics (specifically Niels Bohr's philosophy-physics) and scholarship from feminist and critical theory traditions, most importantly Butler, Foucault, and Haraway.[80] For Barad, a posthumanist reformulation of Judith Butler's performativity concept[81] calls into question the idea of a pre-existing human-animal divide.[82] Instead, it analyses material-discursive practices as producing different divides in instances of intra-action. From this perspective, what an animal (or human, or test, or alternative) is (and is not) does not precede research practice, but boundaries are produced by material-discursive practices—that is, they are iteratively (re)produced and reconfigured in instances of performed intra-actions.[83]

In their article Animal Performances, Birke et al. engage with Barad's posthumanist performativity to look at dyads of human and nonhuman animals. Specifically, they consider the dyad lab rat and scientist. Laboratory rats and scientists are not seen to pre-exist the practice of animal testing. Rather, they emerge out of a choreography involving rats, humans, and technologies, as hybrid phenomena.[84] Intra-actions that

77 Wolfe, Human, All Too Human, 572.

78 Birke et al., Animal Performances; Gregory Hollin and others, '(Dis)Entangling Barad: Materialisms and Ethics', Social Studies of Science, 47.6 (2017), 918–41 <https://doi.org/10.1177/0306312717728344>.

79 Hollin et al., (Dis)Entangling Barad.

80 Karen Barad, Meeting the Universe Halfway: Quantum Physics and the Entanglement of Matter and Meaning (Durham, NC, [etc.]: Duke University Press, 2007).

81 Butler originally used the concept of performativity to show how "queering" is a doing, rather than the word "queer" being a representation of a pre-existing reality. Judith Butler, 'Critically Queer', GLQ: A Journal of Lesbian and Gay Studies, 1.1 (1993), 17–32 <https://doi.org/10.1215/10642684-1-1-17>.

82 Karen Barad, 'Posthumanist Performativity: Toward an Understanding of How Matter Comes to Matter', Signs: Journal of Women in Culture and Society, 28.3 (2003), 801–31 <https://doi.org/10.1086/345321>; Barad, Meeting the Universe Halfway.

83 Ibidem.

84 Birke et al., Animal Performances.

make up this choreography can reproduce as well as challenge a human/animal dichotomy, showing how this dichotomy is not 'natural' or pre-given. At the same time, this dichotomy can become relatively stable through an iterative process of congealment, and consequences for individual lab animals can be irreversible.

According to Birke et al., this performative approach is more inclusive of nonhuman animals, because it allows for nonhuman agency and is focused not on language but on doings. Nonhuman animals are seen as active participants whose behavior matters. Performativity also allows for an analysis of the workings of power as part of the laboratory choreography. Birke et al. emphasize how 'animality' is complex and constructed, just like gender and humanity.[85] It is a relational concept that is performed, not in isolation, but embedded in socio-cultural power relations. These socio-cultural power relations may significantly constrain the possible 'moves' within the multispecies choreography from which the lab animal emerges. The importance of considering that which is excluded from being possible is emphasized by Hollin et al.

Hollin et al. discuss the work of Karen Barad on posthumanist performativity and its potential for moving towards a posthumanist ethics.[86] At the end of their article, they argue that the 'radical potential' of agential realism is often missed, because scholars taking up Barad's approach focus too much on questions of entanglement and not enough on questions of exclusion.[87] Like other scholars, Barad foregrounds entanglement, nonhuman agency, and reality as performed, rather than as pre-existing interactions. Likewise, similar to many other posthumanist and STS approaches, Barad challenges dualisms such as human/animal, nature/culture, and object/subject. However, according to Hollin et al., Barad's posthumanism goes further than this:

> The ethical significance of agential realism, therefore, is not just in extending the idea that things 'could have been otherwise' to the ontological realm, but in conceptualizing the precise moments at which things congeal 'as they are' by understanding the processes through which particular material properties emerge and other realities are excluded from being.[88]

This process of congealment is vital; it means that worlds that have become are relatively stable and that cuts[89] which were made often cannot be reversed. This implies that accountability is required, not only for the intra-actions which are included in the world, but also for possible worlds that are excluded. They propose therefore that we pay more attention to the worlds that are excluded from being. Such an approach can reveal that '[...] certain responsibilities and manifestations of agency could have already been foreclosed by a succession of cuts'.[90] In the context of animal experimentation, this would mean not only accounting for what happens in the laboratory—the bodily entan-

85 Ibidem.

86 Hollin et al., (Dis)Entangling Barad.

87 Hollin et al., (Dis)Entangling Barad, 932.

88 Ibidem, 933.

89 Agential cuts are ontological separations, 'one part of the universe making itself intelligible to another part'. This is an ongoing process of iterative materialization and not a cut existing in a pre-determined reality. Barad, Meeting the Universe Halfway, 176.

90 Hollin et al., (Dis)Entangling Barad, 935.

glement of humans and other animals—but also for worlds that did not become (e.g., a world in which these nonhuman animals were not tested upon), as well as paying attention to response-abilities foreclosed for human and nonhuman animals in the animal laboratory. Specifically for historical work, this would mean focusing on what has remained stable/congealed over time in addition to how practices were reconfigured.

Summary & Takeaways

There are many different posthumanist approaches currently being practiced in research. Of interest to this thesis are those critical posthumanist approaches that are aimed at decentering the human both in theory and in practice and that question the human and humanist concepts and methods. In these approaches, human and nonhuman animals are not fixed, pre-existing entities; they become intra-actively through boundary making practices. For nonhuman animal testing more specifically, the lab animal is a hybrid phenomenon that emerges out of intra-actions between humans, nonhuman animals, and technologies. The posthumanist works by Hollin et al. and Birke et al. above proposed attentiveness towards power relations and processes of congealment, foreclosure, and exclusion, and the effects thereof on individuals' experiences and possible manifestations of agency. Posthumanism additionally challenges historians to think about the (post)humanism of their internal disciplinarity.[91]

1.6 POLITICAL PHILOSOPHY AND THE 'POLITICAL TURN' IN ANIMAL STUDIES

As the previous sections have hopefully made clear, a multispecies history of animal experimentation which moves beyond anthropocentrism needs to account for the impact of structural forces on interspecies relations in the laboratory. Social and political contexts, such as interspecies power relations are important to consider when trying to understand interactions between humans and nonhumans. This is a question with which the 'political turn' in animal studies concerns itself. The political turn, though characterized differently by different scholars, is concerned with applying political theory to interspecies relations and ethics.[92] The main focus of the political turn is not the (ethics of) interaction between individuals of different species but the '[...] moral dimensions of the social and political contexts that structure interactions between humans and nonhuman animals'.[93]

In her work on interspecies democracies, Eva Meijer follows Donaldson and Kymlicka in making a distinction between agency on the micro-level (e.g., affecting one's day-to-day interactions) and the macro-level (affecting key factors such as where one lives

91 Wolfe, Human, All Too Human, 567.

92 Will Kymlicka, '[Review] Robert Garner and Siobhan O'Sullivan (Eds). The Political Turn in Animal Ethics. Rowman and Littlefield, 2016.', Animal Studies Journal, 6.1 (2017), 175–81; Eva Meijer, 'Interspecies Democracies', in Animal Ethics in the Age of Humans: Blurring Boundaries in Human-Animal Relationships, ed. by Bernice Bovenkerk and Jozef Keulartz, The International Library of Environmental, Agricultural and Food Ethics (Cham: Springer International Publishing, 2016), pp. 53–72 <https://doi.org/10.1007/978-3-319-44206-8_4>; Tony Milligan, 'The Political Turn in Animal Rights', 2015; Jason Wyckoff, 'Hierarchy, Global Justice, and Human–Animal Relations', Journal of International Wildlife Law & Policy, 19.3 (2016), 236–55 <https://doi.org/10.1080/13880292.2016.1204884>.

93 Wyckoff, Hierarchy, 236.

and with whom) and emphasizes the importance of considering both. '[...] if we only focus on micro-agency, the subordinate position of animals is not challenged. Because of human dominance, currently they cannot make decisions concerning the larger dimensions of their lives [...]'.[94] For Meijer, nonhuman animals are political agents capable of participating in democratic practices. Currently, however, they are silenced politically.[95] Their silence is not because of some innate quality of nonhuman animals but because of human dominance. Considering nonhuman animals to be political agents would thus add to the excluded worlds that we account for (e.g., if we never think of mice as political agents capable of macro-agency, we also do not account for the excluded world in which they could have had a say in whether or not they should be research animals).

The 'political turn' is aligned with posthumanist critiques of animal rights discourse as being anthropocentric and problematic for seeing living beings as atomistic individuals rather than relational beings.[96] Animals (including humans) are relational creatures and '[...] global justice need not and should not imply an absolutist universalism about the application of anti-hierarchical moral ideals'.[97] According to Meijer, different (groups of) animals have different needs in and ways of communicating. An interspecies democracy should therefore be pluralistic to include a large variety of voices and ways of including those voices. Armstrong warns against the anthropocentrism of respecting animals for their likeness to humans rather than their differences from them, proposing a postcolonial approach to interspecies encounters: 'Encountering the postcolonial animal means learning to listen to the voices of all kinds of "other" without either ventriloquizing them or assigning to them accents so foreign that they never can be understood'.[98]

Summary & Takeaways

The 'political turn' in animal studies considers how social and political contexts, including power relations, structure interspecies interactions. The concepts of micro- and macro-agency are employed to show how these structural dimensions have effects on nonhuman manifestations of agency on different levels, the macro-level being one that is often overlooked. Power hierarchies are not seen as operating monolithically, but rather as operating differently in different time periods and local contexts. As in posthumanism, animals are seen as both relational and political creatures who have the potential to engage in democratic practice.

94 Meijer, Interspecies Democracies, 66. See also E.R. Meijer, Political Animal Voices, 2017 <https://dare.uva.nl/search?identifier=7c9cfda4-560d-4d67-94ea-7bdda29554c9>, 88 & 108-109 and S. Donaldson and Will Kymlicka, 'Rethinking Membership and Participation in an Inclusive Democracy: Cognitive Disability, Children, Animals', in Disability and Political Theory, 2016, pp. 168–97 <https://doi.org/10.1017/9781316694053.009>.

95 Kymlicka, [Review] Robert Garner.

96 Meijer, Interspecies Democracies; Milligan, The Political Turn.

97 Wyckoff, Hierarchy, 252.

98 Philip Armstrong, 'The Postcolonial Animal', Society & Animals, 10.4 (2002), 413–19 <https://doi.org/10.1163/156853002320936890>, 417. On practicing 'epistemic humility' in relations with other animals, see also Simon Burton and Emily Brady, 'What Is It Like to Be a Bird? Epistemic Humility and Human-Animal Relations', in Animal Ethics in the Age of Humans: Blurring Boundaries in Human-Animal Relationships, ed. by Bernice Bovenkerk and Jozef Keulartz, The International Library of Environmental, Agricultural and Food Ethics (Cham: Springer International Publishing, 2016), pp. 89–101 <https://doi.org/10.1007/978-3-319-44206-8_6>.

1.7 CONCLUSION

As stated in the introduction, this historical thesis is based on empirical material: I neither test a specific theory nor depart from a specific theory in analyzing data. However, the theories I discussed above affected the choices I made as a researcher and therefore it is important to make them as explicit as possible. I do this not only to help the reader's understanding and take responsibility as a researcher by accounting for the choices I have made, but also to potentially contribute to furthering the animal turn in history. Below, I will first discuss the theoretical underpinnings I incorporate from the previous sections' discussion and then will specify how this has been translated in my choices of case studies, chapters, and the approaches taken within these chapters. Finally, I will describe the methods I used.

From the animal turn, I take with me the message that historians have an important role in deconstructing the human/animal divide and decentering the human in history to work towards a post-anthropocentric future. This means taking nonhuman animals seriously as subjects and individuals. Understanding more about their daily lives and histories is in itself a worthy goal for historians, regardless of how this contributes to a better understanding of human history (though I would argue that one cannot be done without the other). The literature from STS and posthumanism is instructive for taking a detailed look at daily laboratory practices, so that we can see both human and nonhuman animals as embodied individuals that are co-constituted in interaction. From CAS, critical posthumanism (as proposed by Hollin et al.), and political science I take away the importance of including the macro-level and macro-agency, meaning that I will also look at regulations, politics, economy, networks of companies, government, academia, and broader socio-cultural power relations, how these have developed over time, and how they have interacted with the micro-level of the laboratory. I thus use analytical tools and concepts from all theoretical approaches described earlier. This does not mean, however, that I take no position in the debates between these approaches. How I use and combine these tools and concepts reflects on the importance I attribute to the role of power relations (including domination) in analyzing foreclosures and to recognizing nonhuman animals as political actors. This has consequences for the questions asked and therefore also for possible outcomes of this research. For example, I can only find that nonhuman animals are excluded from political decision making about nonhuman animal experimentation because I recognize them as political actors.

As argued within STS, telling the stories of the micro-level can be valuable to countering the objectification of nonhuman animals. I agree that showing nonhuman animals as subjects has its value, since it is still common to objectify them (especially in animal testing, when they are often spoken of in numbers). Following Specht, the focus should not be on demonstrating that they have agency but rather on how their lived experiences have been affected by structural constraints. This is especially relevant in cases of interspecies entanglement in the laboratory, where interspecies power relations are extremely asymmetrical, and many nonhuman response-abilities and manifestations of agency have likely been foreclosed due to these constraining power relations. This dual focus on day-to-day interactions in specific times and places and broader trends within macro-level structural forces also makes possible the historical contribution (as described by Hilda Kean) of furthering the understanding of the human/animal divide as constantly being re-constructed. Time and space specific human-animal emergences

can be shown to be varying, weakening dualisms and help us to think about which specific contexts would be conducive to different interspecies relations. At the same time, we can identify continuities, that have emerged through an iterative process of congealment. We will see for example that anthropocentrism has remained a relatively stable factor throughout the period being researched but that there were also changes within anthropocentrism and the ways it has played out in different periods and localities.

The content of the six chapters to follow has been described in the introduction. As I stated there, I made the choice to include chapters on both specific groups of nonhuman animals and chapters focusing on regulations, politics, and broader society. Within the chapters on mice and monkeys, I provide thick descriptions of the lives of these animals in order to do as much justice to them as subjects and individuals as the material allows. To move beyond entanglement, the specificities of their day-to-day lives and how these changed (or did not) for different generations of mice and monkeys are related to broader trends and structural forces. A focus on mice and monkeys does not mean that 'the human' is left unexamined. In the multispecies practice of animal experimentation, both human and nonhuman animals affect and adapt to one another, for example through the process of bodily attunement described in both these chapters.

Structural forces relating to politics, economy, and society are examined further in chapters 2 and 4. While these chapters do not feature nonhuman animals as individuals, I argue that they are crucial for understanding the lived experiences of (non)human animals described in the other chapters. To make sure that the connection is clear, I reflect on the meaning of the developments described in these chapters for nonhuman animals in experimental settings, making sure to pay attention to both reconfiguration and stabilities.

1.8 METHODS

Decentering the human in historical research is not without its methodological challenges.[99] I am human, the sources left behind were generally created by humans, and these humans and I are shaped by a world where anthropocentrism is ubiquitous.[100] However, as Benson and Woods argue, human histories are always multispecies histories and thus there must be traces of the nonhuman within sources, even if they are seemingly only about humans.[101] To uncover these, we have to make an effort to 'dig deep' for the animal in the archive.[102] Both the role of the historian, in this case myself, and how sources are used are crucial in writing multispecies histories. As Kean suggests: 'The focus then for animal–human historiography, I am arguing, is not upon materials as such (or the connotations of those materials constructed by humans) but the function of the history writing and the role of the historian'.[103] As has been made

99 Benson, Animal writes; Duxbury, Animal, Gender and Science; Kean, Challenges for historians.

100 Jozef Keulartz and Bernice Bovenkerk, 'Changing Relationships with Non-Human Animals in the Anthropocene—An Introduction', in Animal Ethics in the Age of Humans: Blurring Boundaries in Human-Animal Relationships, ed. by Bernice Bovenkerk and Jozef Keulartz, The International Library of Environmental, Agricultural and Food Ethics (Cham: Springer International Publishing, 2016), pp. 1–22 <https://doi.org/10.1007/978-3-319-44206-8_1>.

101 Benson, Animal writes; Woods et al., Animals and the shaping of modern medicine.

102 Duxbury, Animal, Gender and Science.

103 Kean, challenges for historians, 64.

explicit in the previous sections, my aim to write multispecies histories has affected all aspects of this research; a historian with a different aim would have written a very different thesis, even if using the same sources. This key role of the researcher in knowledge production brings with it great responsibility. Barad points out that this responsibility does not mean that we are somehow in complete control over all aspects of our research: 'We are responsible for the cuts that we help enact not because we do the choosing (neither do we escape responsibility because "we" are "chosen" by them), but because we are an agential part of the material becoming of the world'.[104] Similarly, CAS scholars call for a critical reflection 'on the performativity of its own work and the power relations it produces, reconfigures or challenges'.[105] If I want to challenge rather than reproduce unequal interspecies power relations, this will have consequences for the way I deal with the sources available.

In the absence of live nonhuman animals, 'the animal historian must instead forge a (real, genuine, authentic, ethical) relationship with the embodied traces of past animal life'.[106] According to Benson, this means doing away with certain assumptions about historiographic practice and disciplinary identity, including about the nature of sources used by historians.[107] Whereas Fudge argues that we can only write histories of human attitudes towards nonhuman animals due to the fact that sources are written by humans, Benson argues that if we let go of the strict distinction between real and discursive, things and representations, nonhuman animals and attitudes towards them, we can see that our sources are always more-than-human.[108] This is because everything we do is shaped by our interactions, our becoming together, with other animals. Human-authored texts can then be seen as 'a collection of traces of the animal who writes through the human as well as of the human who writes about the animal'.[109] These traces are perhaps most obvious in visual sources (e.g., pictures of nonhuman animals) but can also be found in textual sources, even in texts not intended to be about nonhuman animals. Finding them requires an active focus on the part of the historian. Privileging nonhuman animals and decentering the human in the questions we ask will help us find these traces. In addition, it can also be revealing to notice the absence of certain nonhuman animals in different sources.[110]

Concretely, all this has meant that I have looked for and selected two case studies for which it was possible to give 'thick' description of a specific group of nonhuman animals: polio-monkeys and XPA-mice. I searched the archives for documents such as lab journals and drawings of cages which gave more information about their daily lives.[111] I also paid specific attention to the absence of nonhuman animals in documents, as well as how they were referred to in different kinds of texts. For a further understanding of interspecies relations, I interviewed respondents who had interacted with one of these two groups of nonhuman animals, explicitly asking them about their relations

104 Barad, Meeting the universe halfway, 176.

105 H. Pedersen and Vasile Stanescu, 'Conclusion: Future Directions for Critical Animal Studies', in Taylor, N. & R. Twine, eds., The Rise of Critical Animal Studies: From the Margins to the Centre, 2014, pp. 262–76, 264.

106 Benson, Animal Writes, 3.

107 Ibidem.

108 Fudge, A Left-Handed Blow; Benson, Animal Writes.

109 Benson, Animal Writes, 5.

110 Duxbury, Animal, Gender and Science; Kean, Challenges for Historians.

111 See Introduction for a description of all sources used.

with them. Images and objects provided further insight into the lives of these past nonhuman animals, not only with regard to their daily lives but to the structural forces that played a role in their lives (one can think for example about the cages in images, who is inside the cage and who is outside, and how this relates to interspecies power relations). These structural forces and the macro-level context in general are explored further using sources such as legal texts and policy documents, where I paid special attention to what these sources have meant for nonhuman animals.

CHAPTER TWO

‘It’s all about better science’. Nonhuman Animal Experimentation and its Alternatives in the Netherlands and at the RIVM: a Broad Historical Sketch.

CHAPTER 2: 'IT'S ALL ABOUT BETTER SCIENCE'. NONHUMAN ANIMAL EXPERIMENTATION AND ITS ALTERNATIVES IN THE NETHERLANDS AND AT THE RIVM: A BROAD HISTORICAL SKETCH.

2.1 INTRODUCTION

It has now, in 2021, been 141 years since the issue of creating national legislation on nonhuman animal experimentation was first introduced in the Netherlands. Since then, many discussions have taken place between scientists, politicians, and animal advocates. The first Animal Testing Act finally came into effect in 1977.[1] The discussions did not end there but continued with each (proposed) revision of the law. These debates were not only about the question of which nonhuman animal experimentation practices should be permissible but also about who should determine this permissibility. Is this something we can leave up to scientists to figure out among themselves? Should the government get involved? What about outsiders such as lay people? These questions have of course been answered differently by different stakeholders, and there have also been changes of perspective within groups of stakeholders, as well as in the general public, over time. For example, legislation and ethical reviews of nonhuman animal experiments have become a widely accepted part of scientific practice[2]; testing cosmetics on nonhuman animals on the other hand has ceased to be considered permissible.[3]

To understand developments in nonhuman animal experimentation and alternatives, we need to consider more than just discussions of legislation and include developments in science and society as well. The 1950s saw the "birth" of Laboratory Animal Science, which had a significant impact on how experiments were performed and therefore also on the lives of nonhuman animals. Care for and welfare of laboratory animals became more prominent from the 1950s onwards, when awareness grew that laboratory animal welfare is important for scientific quality in experiments. Druglitrø writes about the construction of the narrative of "good science" in which "good" refers to both aspects of care and scientific quality.[4] In this narrative, human and nonhuman animal interests are constructed as being interdependent and the focus is on obtaining "good animals", healthy and standardized nonhuman animals that therefore give high quality research results but that also suffer less because they are well cared for.

Where Druglitrø speaks of "good science", the concept of "better science" was more often used by scientists, politician, and activists to promote their own point of view in debates about nonhuman animal testing and alternatives. From the 1980s onwards, the 3Rs (Replacement, Reduction, Refinement)[5] became the dominant discourse in both

1 Ministerie van Binnenlandse Zaken en Koninkrijksrelaties, 'Wet op de dierproeven' <https://wetten.overheid.nl/BWBR0003081/2014-12-18>.

2 Although the extent to which these ethical reviews actually addressed ethical matter is questionable, see chapter 4.

3 For more on EU cosmetics legislation, see: Kristian Fischer, 'Animal Testing and Marketing Bans of the EU Cosmetics Legislation', European Journal of Risk Regulation, 6.4 (2015), 613–21.

4 Tone Druglitrø, '"Skilled Care" and the Making of Good Science', Science, Technology, & Human Values, 43.4 (2018), 649–70 <https://doi.org/10.1177/0162243916688093>.

5 The 3Rs were first described by Russel & Burch in The principles of Humane Experimental Technique, but

Laboratory Animal Science and government policy. "Ethics" also entered the discourse and societal concern for laboratory animals increased, putting pressure on politicians to reduce nonhuman animal testing. Alternatives were presented as the solution to this problem, promising to provide "better science" without using nonhuman animals.[6] Both scientists and activists joined the "alternatives as better science" narrative, with the first group seeing it as a safeguarding of scientific quality and the second as a strategy to achieve what *they* believed to be "better science": science that does not use nonhuman animals.

Despite this "solution" of alternatives however, nonhuman animal testing remained common practice. Recently, a number of scientists have begun to doubt the potential of the 3Rs for achieving further reductions in nonhuman animal testing. They have proposed a new narrative of "better science" which is not based on replacing nonhuman animal tests with an alternative or science that is ethically better but on science that is "better" because it is based on human biology. Hence, as this chapter will show, while the argument of "better science" has been made in different periods and by different stakeholders, making it seem that everyone agrees that it is "all about better science", the meaning of "better" has varied considerably.

I will scrutinize these different meanings of "good science" and "better science" in an analysis of developments in nonhuman animal testing and alternatives across three time periods: 1950–1977, 1978–1997, 1998–2020. For each time period I discuss developments in four areas: nonhuman animals used (numbers/species/origin, etc.), (inter)national legislation and guidelines, Laboratory Animal Science (*Proefdierkunde*), and society (including activism and political discussions). The first aim of this is to provide the background for the following chapters. The second aim is to be able to reflect (in the Conclusion) on both what has changed and on what has remained stable over time in these four areas and how this has affected the lives of tested animals. Before I begin with a discussion of the period 1950–1977, I will set the scene with a brief description of nonhuman animal experimentation before 1950.

2.2 SETTING THE SCENE: NONHUMAN ANIMAL EXPERIMENTATION BEFORE 1950

Despite continuing epistemological differences between scientists about the value of experimentation and vivisection for science, nonhuman animal experimentation became increasingly important in medical research during the nineteenth century.[7] The

only became popular two decades after publication of their book. William M. S. Russell and Rex L. Burch, The Principles of Humane Experimental Technique (London: Methuen, 1959); Jerrold Tannenbaum and B Taylor Bennett, 'Russell and Burch's 3Rs Then and Now: The Need for Clarity in Definition and Purpose', Journal of the American Association for Laboratory Animal Science, 54.2 (2015), 120–32.

6 M. C. Pijnappel, Lost in Technification: Uncovering the Latent Clash of Societal Values in Dutch Public Policy Discourse on Animal-Testing Alternatives ([S.l. : s.n.], 2016) Available online at <https://repository.ubn.ru.nl/handle/2066/151524> [accessed 4 May 2019].

7 Bruno Atalić, 'Historical Development and Ethical Considerations of Vivisectionist and Antivivisectionist Movement', JAHR - European Journal of Bioethics, 3.6 (2012), 399–414; Carin Berkowitz, 'Disputed Discovery: Vivisection and Experiment in the 19th Century', Endeavour, 30.3 (2006), 98–102 <https://doi.org/10.1016/j.endeavour.2006.07.001>.

public displays of vivisection that had previously been common came to an end. Biomedical research moved to the laboratory to become a more systematic endeavor, resulting in a widening of the gap between scientists and the public.[8] The nineteenth century was also the period in which the first anti-vivisection organizations were formed. The Victoria Street Society (now called the Anti-Vivisection Society, (AVS)) was founded in 1875 in the UK, followed in 1890 by the Dutch Society for Fighting Vivisection (*Nederlandse Bond tot Bestrijding van Vivisectie, (NBBV)*) in the Netherlands.[9] The history of anti-vivisectionist organizations in the Netherlands between 1890 and 1940 is described extensively by Amanda Kluveld-Reijerse in her book *Reis door de Hel der Onschuldigen*.[10] She shows that these organizations' concerns were not only related to the welfare of the nonhuman animals used in experimentation but also came from an ambivalence towards science in general and the value of nonhuman animal experimentation in particular, as well as concerns about the morality of vivisection.

During the 1920s, the successes of biomedical research using nonhuman animals made it more difficult to maintain that nonhuman animal testing was useless, and the anti-vivisection movement started losing support in both Europe and the US.[11] Despite diminishing support, anti-vivisectionist organizations remained active and continued to be a cause of concern for researchers, who wanted to avoid negative publicity.[12] In the Netherlands, the NBBV was experiencing internal conflict and some dissenting members left to create the Foundation Anti-Vivisection Society (*Stichting Anti-Vivisectie Bond, (SAVB)*) in 1931. Both organizations together had about five thousand members.[13] Although these organizations were small, they were heard, at least on some occasions, by politicians who were considering the need for nonhuman animal testing regulations.[14]

Anti-vivisectionists also made their voices heard to politicians on the matter of regulations, but they were not successful in arguing their case and the idea of regulation was met with strong opposition from scientists. The first time nonhuman animal experimentation was spoken about in Dutch Parliament was in 1880, when Articles 254 and 455 of the Penal Code were discussed.[15] Members of Parliament asked the Minister to create a special law regulating 'vivisection', similar to the law created in the UK. In 1883 and 1885, the Minister asked scientists if they saw a need for regulations. Both times the response was that there was no such need. The Royal Academy of Arts and Sciences (KNAW*)* stated that any limitation on nonhuman animal experimentation was

8 Atalić, Historical Development; Nuno Henrique Franco, 'Animal Experiments in Biomedical Research: A Historical Perspective', Animals, 3.1 (2013), 238–73 <https://doi.org/10.3390/ani3010238>; Guerrini, A., Experimenting with Humans and Animals. (Baltimore: The Johns Hopkins University Press, 2003).

9 Amanda Alwien Kluveld-Reijerse, Reis door de hel der onschuldigen: de expressieve politiek van de Nederlandse anti-vivisectionisten, 1890-1940, Geschiedenis en gezondheid (Amsterdam: Amsterdam U.P, 2000).

10 Ibidem.

11 Atalić, Historical Development; Guerrini, Experimenting with.

12 Guerrini, Experimenting with.

13 Kluveld-Reijerse, Reis door de hel.

14 R.J.H. Kruisinga, Regelen met betrekking tot het verrichten van proeven op dieren (Wet op de dierproeven), Memorie van Toelichting (zitting 1969-1970 – 10 589), 6. Available online at https://repository.overheid.nl/frbr/sgd/19691970/0000231948/1/pdf/SGD_19691970_0004163.pdf

15 Ibidem, 5. Article 254 prohibited the abuse of nonhuman animals, provided there was cruel intent. This condition of cruel intent made the law inapplicable in situations of nonhuman animal experimentation.

neither necessary nor desirable, since all nonhuman animal experiments being conducted were necessary and no instances of abuse had been found. The medical faculties claimed that regulations would only hinder science and were also impossible to apply in practice, as had been the experience in England and Germany. They argued that since the results of experiments are unknown and often unexpected, it would be impossible to judge the relevance of an experiment in advance. Since neither investigation revealed any nonhuman animal abuse, the minister found it unnecessary to pursue the issue. [16]

Each time legislation was discussed in the decades that followed, scientists again brought forward the argument that regulations would hinder scientific progress. The government formed state committees to investigate the issue in 1907, 1933, and again in 1953. While the first two committees advised in favor of regulations, the last committee did not, swayed by the argument that regulations would form an obstacle to scientific progress.[17]

Thus, despite much discussion, nothing changed within the legal realm for experimental animals during this period. When it came to nonhuman animal use in scientific research, there were however several significant developments. Firstly, there was a strong increase in nonhuman animal experimentation, internationally, in the Netherlands, and at the RIVM.[18] Secondly, the way these increasing numbers of laboratory animals were "produced" changed significantly. The production process was industrialized and focused on creating "standardized" nonhuman animals through inbreeding and selection.[19] The standardization and industrialization of lab mice in the US is described in Rader's work *Making Mice*[20]. Focusing on the Jackson Laboratory, Rader shows how genetic variation in nonhuman animals came to be seen as "noise" which disturbed experiments and how the "production" of lab animals subsequently became similar that of assembly line industries.[21] Similar developments also took place in Europe, albeit a bit later than in the US. Robert Kirk describes the history of the Laboratory Animals Bu-

16 Ibidem, 5.

17 Ibidem, 5-6; Cock Smit, Dierproeven: 100 jaar discussie (Kampen: La Rivière en Voorhoeve, 1989).

18 The earliest estimate available is from 1907, when it was found that about one thousand animals were used in experiments per year in the Netherlands (Kluveld-Reijerse, Reis door de hel). Lack of registration makes it difficult to say much more about developments in the number of nonhuman animals used other than that numbers increased in the first half of the 20th century, both (inter)nationally and at the RIVM. Data for the UK shows a growth in the number of nonhuman animal experiments from 1920 onwards, accelerating after World War II. Andrew N. Rowan, Of Mice, Models, and Men: A Critical Evaluation of Animal Research (SUNY Press, 1984). The RIVM had to build new housing to make space for larger numbers of animals in 1936. Henk van Zon, Tachtig jaar RIVM (Van Gorcum, 1990). At the Dutch Cancer Institute, Korteweg had started to breed inbred mice in 1932; at the time, they were already being bred at an industrial scale in the US. In 1936, Korteweg had more than five thousand mice and by 1950 had fifty thousand. J. Lesterhuis & E.S. Houwaart, Bringing the inbred-mouse to Europe-The Netherlands Cancer Institute within the context of international cancer research 1913-1950. In WU Eckart (ed). 100 Years of organized cancer research - 100 Jahre organisierte Krebsforschung. Georg Thieme Verlag, Stuttgart, 2000.

19 Gail Davies, 'Mobilizing Experimental Life: Spaces of Becoming with Mutant Mice', Theory, Culture & Society, 30.7–8 (2013), 129–53 <https://doi.org/10.1177/0263276413496285>.

20 Karen A. (Karen Ann) Rader 1967-, Making Mice: Standardizing Animals for American Biomedical Research, 1900-1955 (Princeton: Princeton University Press, 2004).

21 Ibidem; Karen Rader, 'The Mouse's Tale: Standardized Animals in the Culture and Practice of Technoscience', Cabinet Magazine, 4 (2001) <http://cabinetmagazine.org/issues/4/rader.php>;

reau, established in the UK in 1947.[22] This bureau was created in order to develop national standards for lab animals to improve the quality of nonhuman animals supplied by commercial breeders. As we will see in the next section, it also played a major role in the establishment of "Laboratory Animal Science" in the 1950s. In the Netherlands, the Central Lab Animal Facility was established in 1948, which was also aimed at improving the quality of supply of lab animals.[23] While in Europe standardization through inbreeding did not become the practice until the 1950s, there were some exceptions. In the Netherlands, pathologist Korteweg started inbreeding with mice he received from the Jackson Laboratory and, by 1950, he had produced around fifty thousand mice.[24]

In summary, when the Netherlands entered the 1950s nonhuman animal experimentation was expanding rapidly and increasingly using standardized nonhuman animals, whose "production" was moving towards an industrial scale. There was no legislation on nonhuman animal testing and opposition to nonhuman animal experimentation was present but limited. The successes in biomedical research had contributed to a more positive attitude towards science from the general public. The country was of course also preoccupied with rebuilding itself after the Second World War, which had put the issue of human experimentation high on the agenda—a development that was not without consequence for nonhuman animals.

2.3 'GOOD ANIMALS': EXPERIMENTATION ON GROWING NUMBERS OF HEALTHY AND STANDARDIZED NONHUMAN ANIMALS (1950–1977)

In this section, I discuss the developments in nonhuman animal experimentation and alternatives from the 1950s to 1970s by analyzing significant developments in nonhuman animal use, law, Laboratory Animal Science, and public attitudes. The period is characterized by a steep increase in nonhuman animal use, a change in attitudes towards legislating nonhuman animal testing, the "birth" of Laboratory Animal Science, and changing public attitudes regarding science and public health.

22 Robert G. W. Kirk, 'A Brave New Animal for a Brave New World: The British Laboratory Animals Bureau and the Constitution of International Standards of Laboratory Animal Production and Use, circa 1947–1968', Isis, 101.1 (2010), 62–94 <https://doi.org/10.1086/652689>.

23 H.W. Lintsen (editor), J.L. Schippers and others, Tachtig jaar TNO (TNO, 2013). Available online at https://pure.tue.nl/ws/portalfiles/portal/109401403/Harry_TACHTIG_JAAR_TNO_digitaal_.pdf

24 Lester & Houwaart, Bringing the inbred mouse to Europe. In their article on inbred mice cancer research in the Netherlands, Lesterhuis and Houwaart describe how in the 1910s and 1920s, American researchers focused on the genetics of cancer, whereas European research focused on exogenous factors. For their genetics research, American scientists started to breed inbred-mouse strains, consisting of thousands of mice. Through cross-breeding, mouse strains were obtained that had high occurrences of tumors. In Europe, in contrast, it was common to use small populations of heterogenous mice. However, the Dutch Cancer Institute was an exception to the European trend. Pathologist Remmer Korteweg was in contact with American researcher Clarence Little of the Jackson Laboratory where, in the 1930s, producing inbred mice reached industrial scales of a few hundred thousand per year. Korteweg received specimen of two mouse strains and started breeding them in Amsterdam. According to Lesterhuis and Houwaart, Korteweg played an important role in making inbred mice the standard in Europe, as it already was in the US, by sending around specimens of his mice and showing researchers around in his institute. The inbred mouse was not only useful because of the high occurrence of tumors but also seen as a solution to the issue of variability in experimental results.

2.3.1 The Nonhuman Animals

Worldwide the number of nonhuman animals used in research grew steeply between 1950 and the late 1970s.[25] Although no data is available for the Netherlands specifically, there are indications of increased nonhuman animal use in research during this period. In 1948, the National Central Lab Animal Facility (*Centraal Proefdierenbedrijf, (CPB)*) was created to provide research institutes with laboratory animals. Already in 1951, in 1956, and again in the 1960s, there was the need to expand the CPB to meet growing demand.[26] Rowan estimates that half a million nonhuman animals were used in experiments in 1960 in the Netherlands.[27] A survey by the Dutch government in 1962–1963 led to an estimated 1,175,000 'warm-blooded' nonhuman animals and 1.5 million 'cold-blooded animals or multicellular invertebrates' being used in experiments in 175 laboratories.[28] The second group included reptiles, fish, frogs, and insects; numbers were not specified further. The first group included nonhuman animals from many different species. Smaller animals such as mice, rats, guinea pigs, hamsters, ferrets, and rabbits made up the bulk of the lab animals that were used—about 870,000 per year in 150 laboratories. Animals typically used in nonhuman animal agriculture, such as horses, cows, and sheep, were used in 12,000 experiments. In addition, about 2.5 million birds were used, about 6,000 dogs and cats, and 1800 monkeys (1550 of whom were used to produce the polio vaccine).[29]

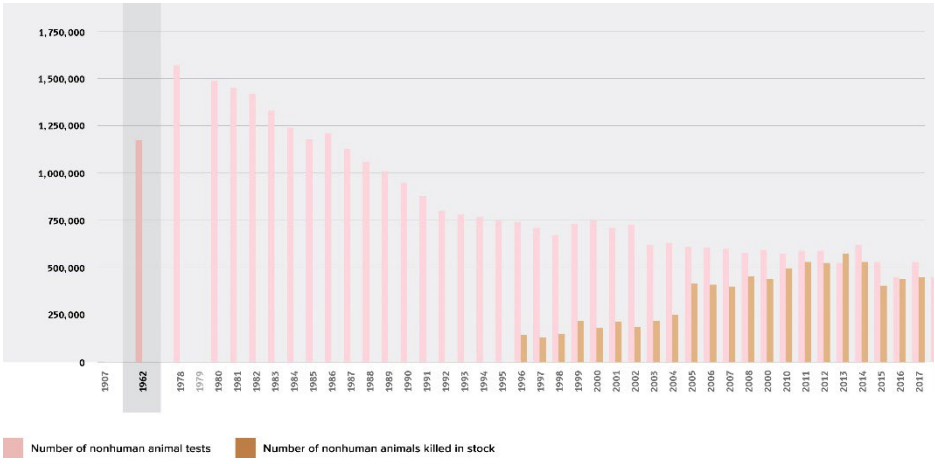

Figure 2.1 Number of nonhuman animal tests and nonhuman animals killed in stock in the Netherlands 1907-2019: 1950-1977[30]

25 Rowan, Of Mice.

26 Ontwikkeling van de Proefdierkunde in Nederland., by Gulden, W.J.I. van der & Gaalen, J.M. van (Eds.); Nieuws van het centraal proefdierenbedrijf TNO, Kontakt TNO, 11:4 (April 1967), 65-66. Available online at https://docplayer.nl/45319111-Kontakt-april-jaargang-ii-nummer-4.html.

27 Rowan, Of Mice.

28 Tweede Kamer Stukken, verslag 19e vergadering 1964-1965 (15/12/1964), 768.

29 Ibidem.

30 Sources: Kluveld-Reijerse, Reis door de Hel; Tweede Kamer Stukken, verslag 19e vergadering 1964-1965 (15/12/1964), 768; Veterinaire Hoofdinspectie van de Volksgezondheid. Sectie Dierproeven and Nederlandse Voedsel- en Warenautoriteit., 'Zo doende ...: jaaroverzicht door de Sectie Dierproeven van de Veterinaire Hoofdinspectie

The number of nonhuman animals being used grew to about 1.5 million in 1978, the first year during which nonhuman animal experimentation registration occurred in the Netherlands.[31]

Very little data is available for nonhuman animal use at the RIVM. A monthly report of the RIVM Department for Serum and Vaccine Preparation (*SVB* in Dutch) listed nonhuman animals used in May 1962: 5530 mice, 1948 guinea pigs, and 37 rabbits (total: 7,515).[32] Most of these nonhuman animals were used for preparing the pertussis (whooping cough) vaccine and for the purification of vaccines. Since this is only one of RIVM's departments and use may have varied greatly between months, an estimate for the yearly use in 1962 cannot be made based on this information. For guinea pigs, annual numbers are available for 1962. A memo regarding the supply of laboratory animals details that in 1962 the demand for guinea pigs was 18,000 and that 16,000 of these were bred at the RIVM. The remaining 2,000 were purchased from the Central Lab Animal Facility.[33] A short yearly report published in *Biotechniek* stated that the laboratory animal department of the RIVM had thirty employees in 1964 and had bred the following nonhuman animals: 219,526 mice, 2,961 rabbits, 18,810 guinea pigs, and 3,088 rats. In addition, the institute purchased: 3,061 monkeys, 97 cats, over 2,000 guinea pigs, and 669 rabbits, as well as a number of calves, sheep, horses, pigs, and poultry (numbers not specified), for a total of more than 250,212 nonhuman animals that year.[34] Official annual numbers for the RIVM are only available from 1978 onwards; in 1978, 246,468 nonhuman vertebrates were used in experimentation.[35] Invertebrates were not counted in the official national registration that started in 1978.

2.3.2 Law

In 1954, a dedicated committee of the Dutch Health Council concluded on the basis of a survey that there was no reason to create nonhuman animal testing legislation. However, the Minister of Social Affairs and Public Health did not want to give up on the idea of licensing and legislation altogether and considered making this part of the nonhuman animal protection law but in the end decided that more time was needed to research the matter. In 1961, the Minister promised Parliament that the issue would be investigated, both in the Netherlands and abroad, and an interdepartmental working

van de Volksgezondheid over het jaar ...', series 1978-2021. Please note that the data shown in this graph come from a variety of sources and measurements instruments and definitions used very between these sources. In addition, the registration method used by the Dutch government from 1978 onward, has also been adjusted several times. This means that the bars in this and the following graphs depicting numbers of nonhuman animal tests, are not one hundred percent comparable and the graphs should only be seen as indicating general trends in nonhuman animal use over time.

31 Registration was still voluntary that year, so this could be an underestimation. Also note that it is the number of experiments that is registered—the actual number of nonhuman animals used is slightly lower, since a small percentage of animals is re-used.

32 Maandverslag SVB, mei 1962. Proefdieren; Bestellen proefdieren via afd Proefdiervoorziening 1959/64. RIVM Archive, file no.1021295.

33 Proefdieren; Bestellen proefdieren via afd Proefdiervoorziening 1959/64
Memo 13/7/1962. RIVM Archive, file no.1021295.

34 Jaarverslagen TNO, R.I.V., C.D.L., Biotechniek, 1965, 123-125.

35 B.C. Kruijt & R. Boot, Proefdiervoorziening: kweekmethoden, 11/11/1985. RIVM Archive, file no. 1018991.

group was created to conduct this research.[36] The working group held a survey in 1962 and 1963 of 175 institutes to find out how many nonhuman animals were being experimented upon annually in the Netherlands as well as about the use of (full) anesthetic and pain relief. In their report, the committee concluded that the number of nonhuman animals used was not unreasonable and that there were no signs that pain relief and full anesthetics were used insufficiently. While several members of Parliament saw grounds in this report to develop legislation, the state secretary wanted the committee to conduct further research into the matter in other countries and gave order to do so. In 1966, the committee presented their next report in which they concluded that all Western European countries surrounding the Netherlands had some kind of regulation of nonhuman animal experimentation and that there were several reason for creating such a regulation in the Netherlands as well: the nonhuman animals needed to be protected as much as possible, nonhuman animal experimentation was likely to increase as science progressed, housing for nonhuman animals should be improved, regulation would (by requiring registration) create an overview of developments in nonhuman animal testing, and legislation could help researchers legitimize their research if they were criticized. Based on this report, legislation was proposed and presented to the Central Council for Public Health. A consultation process followed in which both scientists and animal protection organizations were heard.[37] In 1970, a proposal for the Animal Testing Act was sent to Parliament. This proposal was met with strong opposition from medical scientists, who saw the licensing system as criticism on their work and argued that the Act would cause research to move abroad. Seven years of debate followed, and in 1977 consensus was finally reached and the first Dutch Animal Testing Act was accepted.[38]

Legislation also played a role in increasing nonhuman animal testing. After the atrocious experiments on humans during World War II, regulations for experimenting on humans became stricter. The Nuremberg Code stated that consent was required for human experiments and that they were only allowed if preceded by nonhuman animal experiments.[39] This does not mean that human experimentation was immediately highly regulated in the Netherlands: government action came later than is usually assumed. Ethical reviews of experiments on humans were for example not included in Dutch law until 1998.[40] The Dutch drug market had been unregulated until then, but this changed with the Drugs Provision Act *(Wet op Geneesmiddelenvoorziening*) which was accepted in 1958 and enacted in 1963.[41] The RIVM already had the task of testing new drugs for their effects, side-effects, and toxicity, and this new law prompted an expansion of their pharmacological laboratory with new equipment. The thalidomide tragedy of 1961 further increased RIVM's workload as drugs now also had to be tested for teratogenic and

36 R.J.H. Kruisinga, Regelen met betrekking tot het verrichten van proeven op dieren (Wet op de dierproeven), Memorie van Toelichting (zitting 1969-1970 – 10 589), 6.

37 Ibidem.

38 Pijnappel, Lost in Technification.

39 Guerrini, Experimenting with.

40 Noortje Jacobs, 'Ethics by Committee: Governing Human Experimentation in the Netherlands, 1945-2000', 2018 <https://doi.org/10.26481/dis.20180620jn>.

41 Ministerie van Binnenlandse Zaken en Koninkrijksrelaties, 'Wet op de geneesmiddelenvoorziening' <https://wetten.overheid.nl/BWBR0002290/2006-03-01>.

mutagenic effects using multiple species of nonhuman animals.[42] All of this contributed to more animals being used in medical research.

2.3.3 Laboratory Animal Science

In the 1950s we see the "birth" of *Proefdierkunde* or Laboratory Animal Science, both in the Netherlands and internationally.[43] The aforementioned Laboratory Animals Bureau in the UK not only focused on national supply of lab animals but also became a major international player, producing standardized lab animals and pioneering Laboratory Animal Science. According to Kirk, standardization discourses and internationalization are inherently linked, and standardization discourses are not only regulative but also productive:

> The discourse of standardization was utilized by diverse parties to enroll the state (in the form of the MRC [Medical Research Council], industry (the producers and suppliers of animals), and biomedical scientists (the users of laboratory animals) within a shared community established by reconceiving laboratory animals as a national and, later, transnational resource'.[44]

Dutch researchers and animal technicians also joined this international community. The Central Laboratory Animal Facility of the Netherlands expanded to supply the country with lab animals. The selection department of the facility set up special breeding programs to create nonhuman animals most suitable for diverse research purposes. Both economic and nonhuman animal welfare reasons were given for centralizing the supply of lab animals. Smaller breeders, it was argued, lacked both the scientific and nonhuman animal care expertise, which would lead to too much wasted "material".[45] Tying up nonhuman animal welfare with efficient use of "resources" (i.e., tested animals) was characteristic for the Laboratory Animal Science in the 1950s and 1960s. Druglitrø describes how, from the 1950s onwards, lab animals were transformed into 'compound objects of care':

> The changes that followed the establishment of laboratory animal science from the 1950s thus transformed laboratory animals from being mere animals to objects that were meticulously measured in terms of disease, health status, and performance and that were very much situated within and products of science. This shift thus also involved a shift in the valuing of laboratory animals. The new animals can be described as compound objects of care, as they were treated both as technology and biology, in other words, as being part of scientific infrastructures but also at the same time part of a biological species. This complex, it was argued, required specific forms of care, performed by specific persons, with specific skills; it required what they called 'skilled care'.[46]

42 Van Zon, Tachtig jaar RIVM.

43 Druglitrø, Skilled Care; L.F.M. Van Zutphen, Proefdieren en Dierproeven (inaugurele rede Rijksuniversiteit Utrecht), 13/11/1985, RIVM Archive, file no. 101402.

44 Kirk, A brave new animal, 63.

45 Schippers et al., Tachtig jaar TNO.

46 Druglitrø, Skilled Care, 655

In other words, for lab animals to "perform" well, it was important that they were of good quality and that they were kept free from diseases. Similarly, Kirk describes how in the UK, laboratory nonhuman animal well-being became a key methodological concern: '[…] animal well-being was reconfigured and transitioned, moving from a language dominated by moral rhetoric into a new form of specialist expertise grounded in pragmatic science. Within this logic, ethical concern became scientific necessity'.[47]

Dutch research institutes started to employ veterinarians to work with their laboratory animals and organizations, and journals for professionals working with lab animals were formed.[48] The first edition of the journal *Biotechniek* was published in 1962.[49] Its aim was to share information about nonhuman animals often used in research and how to best take care of them, often based on international research. The authors of the first edition emphasized the importance of 'skilled care', arguing in several articles that care takers and technicians need to be educated (and receive an appropriate salary), since their work requires not only 'love for the job', but also knowledge, experience, and technical skills. They argued that these professionals are crucial links in scientific research because care for nonhuman animals is in the interest of research: '[…] now that research methods are becoming more and more refined, he [the researcher] needs to have access to animals free of diseases and in the best condition. That only animals in the best condition give the best performance is a truth which is as well-known as it is old'.[50] Taking good care of lab animals was not only seen to require appropriate training, but also technicians and care takers who had an appropriate personalities, including the personality trait 'responsible': 'which makes it impossible for a good animal care taker to leave animals behind without food or water, even if it is already past working hours'.[51] The Central Animal Laboratory in Nijmegen, which published *Biotechniek* in the first years, started a two-year training course for care takers and technicians in 1960 to meet the need for 'skilled care'.[52]

For institutes like the RIVM, ensuring good quality started with thinking about the origin of their lab animals. Within the RIVM, a department of Lab Animal Supply was created and, in 1962, it was agreed that from then on all lab animals had to be purchased through that department.[53] Many lab animals were bred at the RIVM, others were acquired from other breeders, preferably from the CPB. As we will see in Chapter 3 in relation to the 'Polio-monkeys', lab animals were sometimes also obtained from the wild using a commercial import company. The quality of these imported monkeys was often complained about due to many monkeys dying or become ill despite preventive measures (see Chapter 3 for more details).

47 Robert G. W. Kirk, 'The Invention of the "Stressed Animal" and the Development of a Science of Animal Welfare, 1947–86', in Stress, Shock, and Adaptation in the Twentieth Century, ed. by David Cantor and Edmund Ramsden, Wellcome Trust–Funded Monographs and Book Chapters (Rochester (NY): University of Rochester Press, 2014) <http://www.ncbi.nlm.nih.gov/books/NBK189531/>, 249.

48 Gulden & van Gaalen (eds.), Ontwikkeling van de Proefdierkunde.

49 Animal technicians are usually called biotechnici in Dutch; occasionally they are also called zoötechnici. The journal Biotechniek is still published and can be found here: dalas.nl/publicaties.

50 Zorg om het dier, Biotechniek, 1962, 136-139, 139.

51 De opleiding van biotechnici en dierverzorgers, Biotechniek, 1962, 10-13, 12.

52 Ten geleide, Biotechniek, 1962, 1-2.

53 Proefdieren; Bestellen proefdieren via afd Proefdiervoorziening 1959/64, Memo 13/7/1962. RIVM Archive, file no. 1021295.

Measures to prevent diseases were referred to as Microbiological Quality Control, which got increasing attention within the RIVM during the 1960s. In 1962, B.C. Kruijt wrote: 'Now that the problems with the numbers of animals are largely solved, we need more attention for quality, especially pathogens that cause death in mice'.[54] He further stated that in 1961 over 20% of killed mice had pneumonia or an infection of the upper airways.[55] Since the causes were largely unknown, he thought it time to start testing for pathogens.

Another topic frequently discussed within Laboratory Animal Science was that of housing lab animals. In the early 1970s, a working group entitled Lab Animal Housing was formed at the RIVM. This working group discussed housing for nonhuman animals based on their own experiences as well as on (inter)national research (e.g., in *Biotechniek*). They did not only focus on the types and size of cages used to house lab animals but also on hygiene measures (e.g., the working group file includes a very elaborate discussion on the use of disinfectants, which were being applied a bit too generously according to some). In 1974, five rules were formulated regarding the hygiene in animal rooms: 1) no eating or drinking, 2) use separate coats, 3) disinfect hands, 4) disinfect cages before transport, 5) regularly clean the room.[56]

While more attention was being paid to hygiene and disease prevention, there were also practices deemed acceptable that we would frown upon today, such as taking home used rabbits for consumption. A 1960 note regarding 'rabbits' details the distribution system for rabbits that had been bled out (the blood was used in experiments) and given to employees for consumption, about 'nine rabbits per man per month'. It was argued that this distribution should happen justly, taking into account the salary of employees.[57]

During this period, the focus on promoting lab animal health was a matter of efficiency and economics as well as concern for human health, rather than ethical concerns towards lab animals; the idea of ethics would enter the Laboratory Animal Science discourse later.[58]

2.3.4 Society

As we saw in the beginning of this section, nonhuman animal experimentation grew rapidly during the 1950s and 1960s. To understand this, we need to consider public attitudes towards science and health as well as towards nonhuman animals. The biomedical sciences in general grew and there was a greater interest in public health. People feared diseases (such as polio) and toxins, and politicians together with the public turned to scientists to solve the problem.[59] The government became more involved in science and public faith in science increased, although attitudes would become more

54 Proefdieren; Bestellen proefdieren via afd Proefdiervoorziening 1959/64, Letter from B.C. Kruijt (23/02/62). RIVM Archive, file no. 1021295.

55 Ibidem.

56 B.C. Kruijt, verslag vergadering 14/11/1974. RIVM Archive, file no. 1069682.

57 Nota nr. 36/60 Betreft konijnen, 01/09/1960 to Dr. J Spaander from J.T.H. Konter. RIVM Archive, file no. 1021296.

58 Druglitrø, Skilled Care; see also Chapter 3 for a clear example of this shift in thinking regarding the Polio-monkeys.

59 Rowan, Of Mice.

critical again during the 1970s.[60] Many new chemicals were introduced into the market, and people wanted to know if they were safe. The publication of *Silent Spring* in 1962, for example, led to a fear of carcinogens in substances such as pesticides and redoubled public pressure for safety testing.[61] This in turn led to more work in a larger variety of areas for biomedical research organizations such as the RIVM in the Netherlands; its number of employees increased from two hundred in 1950 to one thousand in 1965.[62] The research field expanded even more later on, adding testing of environmental toxins.[63] Another reason that RIVM's nonhuman animal use increased was the National Vaccine Program, which started in 1957 with a quadruple-combination vaccine against diphtheria, pertussis, tetanus, and polio (in Dutch abbreviated as *DKTP*).

During the 1950s and 1960s, there was little opposition against nonhuman animal testing. The NBBV and SAVB (later called AVS) were both still active, but the public in general was mostly quiet. An exception was of course the Thalidomide tragedy of 1961. A hefty debate ensued, with some arguing that the tragedy showed that nonhuman animal testing is useless, while others argued it showed the need for safety testing in more species of nonhuman animals. Eventually, regulations were adjusted to require safety testing of new drugs on multiple species of nonhuman animals.[64] Despite relatively little public opposition to nonhuman animal testing, the Dutch government decided during this period that an Animal Testing Act was needed, and animal protection organizations were included in the legislative process.

Parliament discussed the survey which had been conducted in 1962–1963 about nonhuman animal experimentation in the Netherlands and the press release about that survey on December 15, 1964. The press release, entitled 'Size and manner of experimentation on animals not unreasonable' (*Omvang en wijze van proeven op dieren niet onredelijk)*, claimed that the survey results did not justify legislation.[65] Members of Parliament from different political parties disagreed, for a variety of reasons. Van Dis (Reformed Political Party, *SGP*) cited the suffering of 'creatures of God' as well as the questionable predictive value of research on animals for humans as reasons to limit animal experimentation through legislation and a licensing system. Additionally, this party aligned itself with the anti-vivisectionists in asking for a research position at a

60 For more on public attitudes towards science in the 1970s, see: Mathieu Quet, 'Science to the People! (And Experimental Politics): Searching for the Roots of Participatory Discourse in Science and Technology in the 1970s in France', Public Understanding of Science, 23.6 (2014), 628–45 <https://doi.org/10.1177/0963662512469011>. Specifically for the Netherlands: Joseph Wachelder, Democratizing Science: Various Routes and Visions of Dutch Science Shops. Science Technology Human Values, 2003.

61 Mark Stoll, 'Rachel Carson's Silent Spring, a Book That Changed the World', Rachel Carson Center for Environment and Society, 2012; Karen F. Stein, Rachel Carson: Challenging Authors (Springer Science & Business Media, 2013), 116.

62 Van Zon, Tachtig jaar RIVM.

63 Rowan, Of Mice; Michael D. Waters, Dave Allen, and Mike D. Waters, Reducing, Refining and Replacing the Use of Animals in Toxicity Testing (Royal Society of Chemistry, 2013).

64 For a discussion of the Thalidomide-tragedy and the consequences for regulations on drug safety testing in the Netherlands, see: Toine Pieters, Tussen controle op afstand en betrokken begeleiding Historische trajecten in het Staatstoezicht op geneesmiddelen. In: C. Th. Bakker (ed) Terug naar de Basis; Geschiedenis van het Staatstoezicht voor de inspectie van vandaag. Utrecht: IGZ Kenniscahier, 2010: 49-59.

65 Omvang en wijze van proeven op dieren niet onredelijk, Nederlandse Staatcourant, 1964, nr. 224, 17-11-194.

university in 'homeopathy and vivisection-free medicine', which the Anti-Vivisection Society (SAVB) offered to finance.[66] Bruggeman of the Pacifist Socialist Party (*PSP*), to his own 'great surprise' agreed with Van Dis about the need for a licensing system.[67] He further stated that an animal protection organization should be included and the committee expanded in order to pay more attention to the ethical side of the issue.[68] State Secretary Bartels responded that he had given the committee the assignment of gathering more information both at home and abroad.[69] As it turned out, all the surrounding countries had nonhuman animal testing legislation, and it was decided that an Animal Testing Act should be written. The discussion then moved into what the content of the law should be. Pijnappel has performed an extensive discourse analysis of nonhuman animal testing legislation from 1970 onwards, when the first draft of the Animal Testing Act was presented to Parliament. The analysis shows how the new legislation was presented as a compromise between protecting nonhuman animals and not creating obstacles for scientific practice.[70] This is different from the discourse in Laboratory Animal Science, where scientific quality and animal welfare were constructed as interdependent rather than in opposition. The conflict between human and nonhuman interests is also reflected in the use of term 'necessary evil' to describe nonhuman animal testing, a term first used in the introduction of the 1970 draft Animal Testing Act.[71] The acceptance of this compromise and the resulting Animal Testing Act can be seen as a shift in thinking about nonhuman animal experimentation. However, the compromise still heavily favored human interests, since the new legislation was in no way intended to be a hindrance to scientific research using nonhuman animals or even pose an administrative burden to researchers. In addition, researchers remained responsible for judging the necessity of the experiment.

Summary

During this period, nonhuman animal experimentation came to be seen as "good science" when it protected humans from diseases, toxins, and other dangers and used "high quality" lab animals that performed well. For reasons of performance as well as efficiency, it became more and more important to keep lab animals healthy. This was not done because of ethical considerations about the lab animals as beings with "intrinsic value" (a term that takes the stage next period) for which we have a moral duty to care whether this benefits science or not. The care of lab animals became bound up in the scientific practice of nonhuman animal experimentation because human and lab animal health were constructed to be interdependent.[72] Discussions of ethics or moral duties were not found in the archival material from this period, in contrast to the material from the next period. A reference to ethics was found in the political discussions about legislating nonhuman animal testing. In these discussions, protecting nonhuman animals was sometimes presented as limiting scientific practice and therefore it was opposed by many medical scien-

66 Tweede Kamer Stukken, verslag 19e vergadering 1964-1965 (15/12/1964), 768.

67 PSP was the Pacifist Socialist Party that became GroenLinks (Green Left) in 1990 and generally did not agree with the religious and conservative SGP (Reformed Political Party), hence the surprise.

68 Tweede Kamer Stukken, verslag 19e vergadering 1964-1965 (15/12/1964), 772.

69 Ibidem, 779

70 Pijnappel, Lost in Technification, 65.

71 Ibidem, 63.

72 Druglitrø, Skilled Care.

tists. By the end of the 1960s, however, a majority of politicians agreed that for nonhuman animal testing practices to remain acceptable, legislation would be required.

The aforementioned developments had significant effects on the lives of the nonhuman animals being used in experiments. The measures taken to promote their health meant they were less likely to become ill and/or die of infections during experiments (and consequently of course more likely to die because of the experiment). The focus on using "good animals" (i.e., nonhuman animals that were standardized and healthy) meant more and more nonhuman animals were "produced" in breeding facilities rather than being caught in the wild. This spared many nonhuman animals the traumatic experience of being caught and transported to a laboratory. It also meant more control over every aspect of tested animals' lives, from their birth to their procreation to their death (see Chapter 3 for a more elaborate account of what the switch to a monkey breeding program meant for the lab monkeys). While lab animals had, in the words of Druglitrø, become "compound objects" that need to be well cared for, the object status of nonhuman animals remained unchallenged both within Laboratory Animal Science and in the Animal Testing Act.

2.4 TOWARDS 'BETTER SCIENCE': THE 3RS, ETHICS, AND THE WIN-WIN OF ALTERNATIVES (1978–1997)

> It becomes increasingly clear that the results of animal experiments are influenced among other things, by the presence of species-specific, stable, a-pathogenic microflora in lab animals used. The scientific demand to makes use of SPF-animals for a large part of the research is strengthened by administrative regulations (GMP-GLP) as well as ethical motives (optimal results, no intercurrent deaths, lower numbers).[73]

This quote is from the memo 'Supply of laboratory animals RIVM', written in 1984. The 1980s and 1990s saw important changes in the realms of the law, Laboratory Animal Science, and society in general: the creation of (inter)national regulations and guidelines on nonhuman animal testing, the popularization of the 3Rs (Replacement, Reduction, Refinement), and increased societal and political attention to the ethics of nonhuman animal testing. Below I will analyze these developments to see how nonhuman animal experimentation and alternatives practices changed during this period. I take the acceptance of the first Animal Testing Act in the Netherlands as my starting point. But first, a look at the nonhuman animals who were being experimented upon.

2.4.1 The Nonhuman Animals

In 1978, 1,572,534 nonhuman animal experiments were registered in the first annual registration in the Netherlands. Because of the way the category "animals" is defined in the Animal Testing Act, only experiments with nonhuman vertebrates were registered. Between 1978 and 1997, the number of experiments on nonhuman vertebrates dropped, steeply at first and more moderately in the 1990s.

Nonhuman animal use within the RIVM followed a similar pattern but continued to drop steeply in the 1990s.[74] Throughout this period, mice and rats were the species

73 Notitie proefdierenvoorziening RIVM 4/10/1984. RIVM Archive, file no. 12092.

74 Jaarverslag art 14 funct. WoD NVI, 2007 & 2009; Visie op proefdieronderzoek, 20/01/2005, RIVM Ar-

used most often in experiments both nationally and within the RIVM. The use of nonhuman primates shows a stronger downward trend within the RIVM than the use of other species. This is because most nonhuman primates were used for the production of the polio vaccine and the production process was adapted by RIVM researchers to strongly reduce the number of monkeys required (see Chapter 3). Whereas in 1964, the RIVM still purchased over 3,000 monkeys, only sixty monkeys were used at the institute in 1983.[75] The national use of monkeys did not drop as steeply because from the 1960s onward monkeys were increasingly used for other purposes than the production of the polio vaccine. In the early 1980s, monkey use per year fluctuated between 1,000 and 2,000 (not showing a clear upward or downward trend yet). For example, of the 1,023 monkeys used in 1983, only 182 were used for experiments relating to sera, vaccines, and other biologicals. In comparison, 461 monkeys were used for basic research that year.[76]

Another important development in the use of nonhuman animals in experiments was the creation of the first transgenic animals in the 1980s, first in the US and then, from the late 1980s, also in the Netherlands and at the RIVM. With these transgenic techniques, lab animals were adapted further to the needs of scientists, for example by creating 'oncomice': mice with an activated oncogene which were more likely to develop tumors.[77]

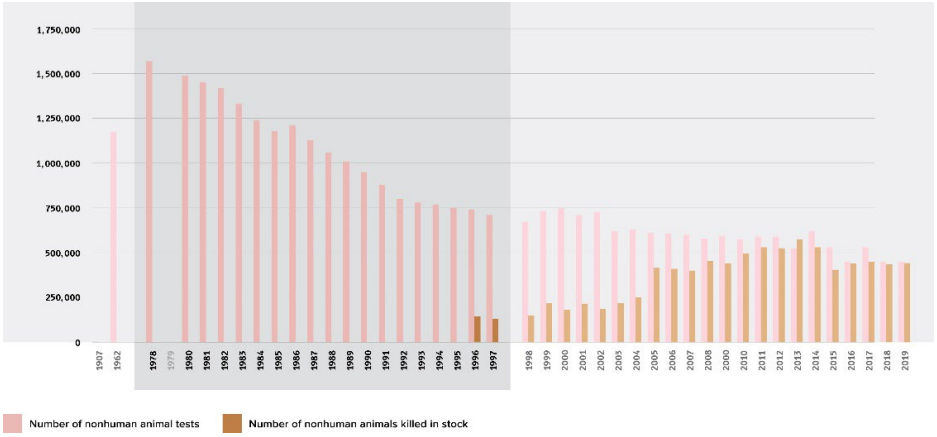

Figure 2.2 Number of nonhuman animal tests and nonhuman animals killed in stock in the Netherlands 1907-2019: 1978-199778

chive, file no. 1215; Jaarverslag art 14 funct. WoD RIVM 1996, RIVM Archive, file no. 1035575; Gebruik proefdieren RIVM, mei 1984, RIVM Archive, file no. 1036416.

75 Gebruik proefdieren RIVM, mei 1984, RIVM Archive, file no. 1036416.

76 Veterinaire Hoofdinspectie van de Volksgezondheid. Sectie Dierproeven., Zo doende 1983: jaaroverzicht door de Sectie dierproeven van de Veterinaire Hoofdinspectie van de Volksgezondheid over het jaar 1983., Volksgezondheidsreeks; ('s-Gravenhage: Distributiecentrum Overheidspublikaties, 1984), 54-55 & 80.

77 Allan Bradley and others, 'Modifying the Mouse: Design and Desire', Bio/Technology, 10.5 (1992), 534 <https://doi.org/10.1038/nbt0592-534>; Douglas Hanahan, Erwin F. Wagner, and Richard D. Palmiter, 'The Origins of Oncomice: A History of the First Transgenic Mice Genetically Engineered to Develop Cancer', Genes & Development, 21.18 (2007), 2258–70 <https://doi.org/10.1101/gad.1583307>. See Chapter 5 for more on the history of transgenic mice.

78 Sources: Kluveld-Reijerse, Reis door de Hel; Tweede Kamer Stukken, verslag 19e vergadering 1964-1965 (15/12/1964), 768; Veterinaire Hoofdinspectie van de Volksgezondheid. Sectie Dierproeven and Nederlandse Voedsel- en Warenautoriteit., 'Zo doende ...: jaaroverzicht door de Sectie Dierproeven van de Veterinaire Hoofdinspectie van

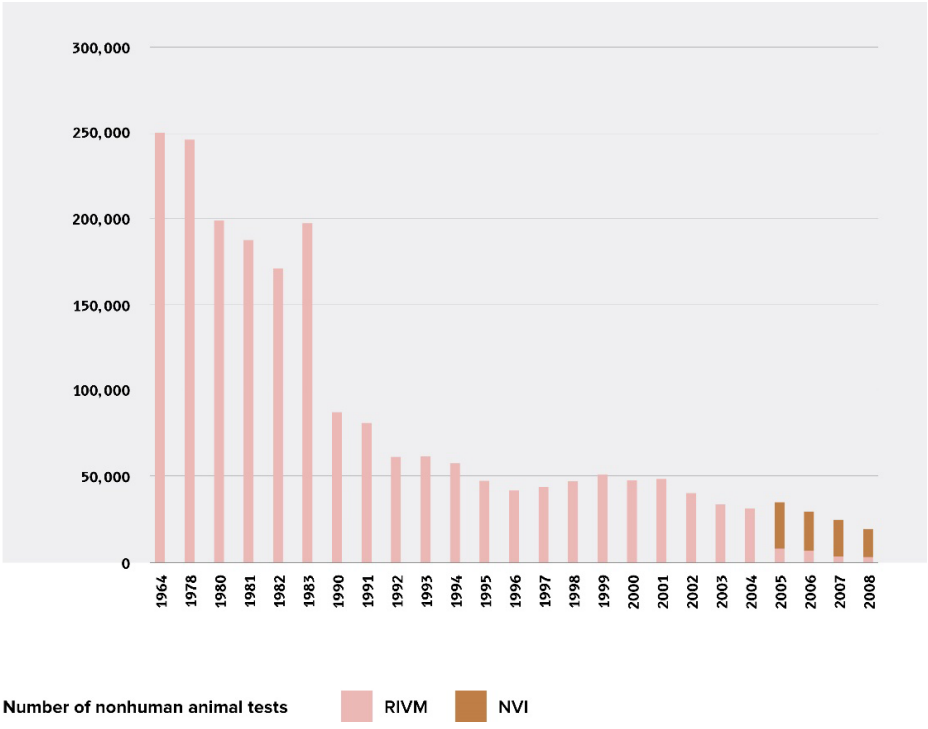

Figure 2.3 Number of nonhuman animal tests at RIVM (1964-2008) and NVI (2005-2008)[79]

2.4.2 Law

The Animal Testing Act (*Wet op de Dierproeven,* (*WoD)*) was accepted in 1977 and enacted in several stages in the years that followed.[80] This law stated that nonhuman animal testing was only to be allowed when no non-animal test was available and when the importance of the test outweighed the suffering of the nonhuman animals being tested. "Animals" in this legal context meant "nonhuman vertebrates".[81] The new law also required all facilities involved in nonhuman animal testing and/or breeding for testing purposes to be licensed and all animal tests (with nonhuman vertebrates) to be registered. The registration was voluntary at first and became mandatory in 1984. The only article of the WoD to come into effect immediately was Article 18, which entailed the appointment of the Committee for Advice for Animal Testing (*CvAvdD* in Dutch, also referred to as Committee Article 18). This committee was tasked with advising the gov-

de Volksgezondheid over het jaar ...', series 1978-2021.

79 Sources: Jaarverslagen TNO, R.I.V., C.D.L., Biotechniek, 1965, 123-125; Jaarverslag art 14 funct. WoD NVI, 2007 & 2009; Visie op proefdieronderzoek, 20/01/2005, RIVM Archive, file no. 1215; Jaarverslag art 14 funct. WoD RIVM 1996, RIVM Archive, file no. 1035575; Gebruik proefdieren RIVM, mei 1984, RIVM Archive, file no. 1036416. Unfortunately, data for the period 1984-1989 could not be retrieved.

80 The last article was enacted in 1986. H.J. Simons, Memorie van toelichting – Wijziging van de Wet op de dierproeven, 1992. Available online at https://www.parlementairemonitor.nl/9353000/1/j4nvgs5kjg27kof_j9vvij5epmj1ey0/vk11nlgu9cy5/f=/kst22485n3k2.

81 Ministerie van Binnenlandse Zaken en Koninkrijksrelaties, 'Wet op de dierproeven' <https://wetten.overheid.nl/BWBR0003081/2014-12-18>.

ernment on all matters related to nonhuman animal testing, for example about ethical review committees.[82] The Veterinary Head Inspector (VHI, later part of the National Food and Goods Authority, (NVWA)) was the government body tasked with monitoring compliance with the law. The VHI also wrote several rules, guidelines, and codes of practice, such as rules for using mice for creating monoclonal antibodies and housing guidelines.[83]

In 1986, the first EU directive on nonhuman animal testing came into effect. In this law, care is given a major role:

> Care is a word which, when used in connection with animals intended for or in actual use in experiments covers all aspects of the relationship between animals and man. Its substance is the sum of material and non-material resources mobilized by man to obtain and maintain an animal in a physical and mental state where it suffers least and performs best in experiments. It starts from the moment the animal is destined to be used in experiments and continues until it is killed by a humane method or otherwise disposed of by the establishment in accordance with Article 9 of the Directive after the close of the experiment.[84]

In this description, the 'scientific mode of care' described by Druglitrø is clearly recognizable: care is in the interest of both nonhuman animals and humans.[85] Nonhuman animals are compound objects that can suffer and that can be disposed of. The EU law also mentioned 'alternatives', stating that:

> The Commission and Member States should encourage research into the development and validation of alternative techniques which could provide the same level of information as that obtained in experiments using animals but which involve fewer animals or which entail less painful procedures, and shall take such other steps as they consider appropriate to encourage research in this field. The Commission and Member States shall monitor trends in experimental methods.[86]

82 These committees are discussed in Chapter 4.

83 Using mice to produce monoclonal antibodies was seen as a particularly distressing experiment, therefore guidelines and restrictions were created in several countries, including the Netherlands. For more on this topic, see C. F. M. Hendriksen and W. de Leeuw, 'Production of Monoclonal Antibodies by the Ascites Method in Laboratory Animals', Research in Immunology, 149.6 (1998), 535–42 <https://doi.org/10.1016/S0923-2494(98)80002-3> and National Research Council (US) Committee on Methods of Producing MonoclonalAntibodies, Animal-Welfare Issues Related to the Ascites Method for Producing Monoclonal Antibodies, Monoclonal Antibody Production (National Academies Press (US), 1999) <https://www.ncbi.nlm.nih.gov/books/NBK100190/>.

84 Annex II: Guidelines for accommodation and care of animals. Council Directive of 24 November 1986 on the approximation of laws, regulations and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (86 / 609 / EEC), Official Journal of the European Communities, L 358 (18/12/1986), 7. Available online at https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:31986L0609&from=EN.

85 Druglitrø, Skilled Care, 653.

86 Council Directive of 24 November 1986 on the approximation of laws, regulations, and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific pur-

Though no explicit reference to the 3Rs is made, the law implied that the concept of 'alternatives' was not limited to non-animal techniques. In fact, the directive only mentioned Reduction (fewer nonhuman animals) and Refinement (less painful procedures), not Replacement. The European law not only emphasized the importance of care, but also introduced an 'Annex of Guidelines for Accommodation and Care of Animals', providing guidelines for things like room temperatures, cage sizes, quarantine period, and 'humane' killing.[87]

The EU law of 1986 required that some changes be made to the Dutch Animal Testing Act. An important legal change came in the Animal Testing Decree of 1993, which added regulations on Animal Experiments Committees (AECs) to the existing Animal Testing Act. These AECs became mandatory for each license holder in 1997, after much discussion between scientists, politicians, and activists (these discussions are analyzed in detail in Chapter 4).

While the law stated that alternatives had to be used when possible, it did not provide much guidance for situations in which there were no non-animal alternatives, and thus judgements had to be made as to whether the benefits of an experiment outweighed the suffering of the nonhuman animals being tested. As State Secretary of Science, Public Health and Culture Joop van der Reijden wrote in 1984: 'It is in first instance the responsibility of the researchers to weigh suffering and interests, the law only provides limited guidance'.[88] He also noted the value of Laboratory Animal Science, which he said had led to 'better and more reliable results, because of which significant reductions in lab animal use have been achieved' and that more progress in this field could lead to even more reduction.[89] Specifically, he aimed for a reduction of 30% in five years.[90]

2.4.3 Laboratory Animal Science

The term *alternatives* is often used to refer to the practice of the 3Rs: replacement, reduction, and refinement, as described in Russell & Burch's 1959 book *The Principles of Humane Experimental Technique*.[91] Interestingly, the authors themselves never used the term "alternatives", and other writers' use of the term varies.[92] The 3Rs became more popular from the 1980s onwards, expanding the meaning of "alternatives" to include reduction and refinement.[93] Waters et al. analyzed the use of 3Rs in toxicology research internationally and described four phases: incubation (1959–1979), increasing acceptance and spread (1979–early 1990s), maturation (early 1990s–2007), paradigm shift (2007–present).[94] The international trend of 3Rs popularization can be seen in

poses (86 / 609 / EEC), Official Journal of the European Communities, L 358 (18/12/1986), 5.

87 Annex II: Guidelines for accommodation and care of animals. Council Directive of 24 November 1986 on the approximation of laws, regulations, and administrative provisions of the Member States regarding the protection of animals used for experimental and other scientific purposes (86 / 609 / EEC), Official Journal of the European Communities, L 358 (18/12/1986), 5.

88 Notitie Dierproevenbeleid, Grondslagen van het Beleid (29/06/1984), 11. RIVM Archive, file no. 1014028.

89 Ibidem.

90 Tweede Kamer Stukken (1984-1985), UCV 98, 19/06/1985, 14. Available online at https://repository.overheid.nl/frbr/sgd/19841985/0000123081/1/pdf/SGD_19841985_0000913.pdf

91 Russel & Burch, The principles of humane.

92 Pijnappel, Lost in Technification; Tannenbaum & Bennet, Russel and Burch's 3Rs.

93 Pijnappel, Lost in Technification.

94 Waters et al., Reducing, Refining and Replacing.

the Netherlands as well and particularly within the RIVM, which positioned itself as an expert on Laboratory Animal Science and was also recognized as such by Dutch politicians and the international community.[95]

In this period, the focus within Laboratory Animal Science was on having a high-quality animal laboratory where nonhuman animals were well cared for. This focus was similar to that of the preceding period, but the field expanded to include attention to more aspects of the lives of lab animals. Caring for nonhuman animals became about more than preventing diseases and high performance and came to include a *moral duty* towards lab animals, not only keeping them healthy but also in a state of general well-being (as far as possible given the circumstances). In addition to measures to improve the animal laboratory, the popularization of the 3Rs also meant more attention to developing alternatives that would replace nonhuman animal tests. For the RIVM, important themes within Laboratory Animal Science included housing, standardized protocols, education, and developing alternatives to replace or reduce nonhuman animal testing.

During the 1980s and 1990s, nonhuman animal experimentation was centralized within the RIVM. First, experiments were clustered per main sector in 1985.[96] In 1989, the institute decided to create one Central Animal Laboratory (*CDL* in Dutch). This was seen as necessary to comply with the demands of the law as well as for reaching efficiency goals.[97] In 1989, EEC and VHI housing guidelines were discussed, resulting in a report with recommendations to improve nonhuman animal housing at the RIVM. Recommended improvements included: bigger cages, different types of cages (makrolon instead of wire cages), social instead of individual housing, and different layouts of the cages.[98] As I will discuss in Chapter 3, researchers even conducted so-called cage preference experiments to find out the preferences of monkey colony members.[99] Some of the new housing requirements were related to hygiene measurements, since compliance with GLP and GMP demanded enough space for hygienic practices (e.g., a sluice to change clothes).[100]

The first two images below show how the housing of rabbits changed at the RIVM between 1950 and 1994. The third image is also from 1994. As you can see, the rabbits in the third image were housed individually in smaller cages, despite changes in housing practices. This was done so that their temperature could be measured constantly. This illustrates that nonhuman welfare interests were not always aligned with human scientific interests and thus welfare measures only applied when possible within the given context of the experiment.

95 Interview R1 & Dollé; Notitie Dierproevenbeleid, Grondslagen van het Beleid (29/06/1984), 11. RIVM Archive, file no. 1014028.

96 Verslag vergadering DEC 19/05/1988, RIVM Archive, file no.1037565.

97 Nota over de herstructurering van de afdeling proefdiervoorziening en de dierexperimentele afdelingen van het RIVM tot centraal dierenlaboratorium and Nieuwbouw proefdierverhuizing (20/04/1989), RIVM Archive, file no. 1037565.

98 Werkbespreking CDF 08/03/89, RIVM Archive, file no. 1037565.

99 E.g. R. Boot, A. van Arnhem, and K. Pots, 'Kooipreferentie Bij Individuele Huisvesting van Java-Apen. 1e Interim Rapport', RIVM Rapport 948473001, 1988.

100 Herhuisvesting en GLP (n.d.), RIVM Archive, file no. 1044271. GLP and GMP stand for Good Laboratory Practices and Good Manufacturing Practices, respectively. GLP were first regulated in the New Zealand Testing Laboratory Act of 1972; GMP were first mandated by the 1962 drug amendments in the US. Jürg P. Seiler, Good Laboratory Practice: The Why and the How (Springer Science & Business Media, 2006); John P. Swann, 'The 1941 Sulfathiazole Disaster and the Birth of Good Manufacturing Practices', Pharmacy in History, 41.1 (1999), 16–25.

Figure 2.4 Rabbit cages (RIVM 1950). Source: RIVM

Figure 2.5 Rabbit cage with refinement and social housing (RIVM 1994). Source: RIVM

Figure 2.6 Rabbit cages with continuous temperature measurement (RIVM 1994). Source: RIVM

Over time, more and more aspects of nonhuman animal experimentation were registered and formalized within the RIVM. In 1979, Kruijt successfully argued that the quality control of lab animals needed to be discussed more structurally within the institute, and the working group Quality Control of Lab Animals was formed as a result.[101] A 1983 memo on GMP stated: 'GMP = working neatly and cleanly' followed by fifteen rules such

101 Verslag vergadering dd. 10 oktober 1979 betreffende kwaliteitsbeheer proefdieren 18/10/1979 by R. Boot, RIVM Archive, file no. 1018991.

as: change coats when entering animal housing, regularly clean floors and drinking systems, do not stack materials against outside walls of animal housing.[102] Somewhat confusingly, the memo concluded with: 'remember: order and cleanliness are the enemies of rats and mice', referring of course not to the *lab* rats and mice but to the free-living rats and mice that were a threat to hygiene.[103] By 1989, a hundred Standard Operating Procedures (SOPs) had been developed and GLP/GMP requirements were being complied with more often.[104] In 1990, the AAP system was put into use, which entailed a standardized and automated central registration of all nonhuman animal experiments within the RIVM.

Figure 2.7 Changing procedure in the staff sluice (RIVM 1988). Source: RIVM.

To ensure lab animal quality, researchers not only looked at preventive measure but also evaluated what happened in cases of nonhuman animal deaths not caused by the experiment. They wrote quarterly reports that listed the causes of intercurrent deaths per species of animals.[105] Most often these deaths were caused by pathogens, but in the case of one monkey the cause of death listed was homesickness.[106] While the situation of a monkey dying of homesickness was rare, it does point out that there is more to caring for lab animals than preventing infections. During the 1980s, promoting the health and welfare of lab animals became about more than just preventing (economic) losses and getting reliable research results; it came to be understood as a moral duty towards

102 Memo W.F. de Graaf Betreffende: GMP = netjes en schoon werken, RIVM Archive, file no. 1017973.

103 Ibidem.

104 Samenvatting CDF journaal 1985-89. RIVM Archive, file no. 1037565.

105 Kwartaalrapportage kwaliteitsbeheer 1983, RIVM Archive, file no.1017973.

106 Ibidem, 12.

the nonhuman animals being experimented upon. As we also saw in the opening quote of this section, ethics became an increasingly important part of this discourse, not separate from scientific concerns but intertwined with them. The health and welfare of lab animals was of interest for nonhuman animals and humans alike but caring for the lab animals was more than just instrumental, it was a moral duty and was affective.[107] Animal technicians and caretakers were the ones caring for the nonhuman animals being tested upon. Their work entailed a lot more than simply implementing the many new protocols and hygiene rules put in place to promote lab animal health and welfare; it required a certain level of affection for nonhuman animals on their part.[108]

While often protocols and affection went hand in hand in caring for the lab animals, on occasion they did not. Such was the case in 1985, when a memo was written regarding pets and GMP/GLP. The memo was stated that pets were a risk for the microbiological quality control of lab animals. Therefore, people who owned commercially acquired rodents or rabbits should not be working with these animals. Department heads compiled a list of all the pets owned by people working in the animal laboratory, showing that over half of them had pets of species that were also used as lab animals. The employee consultative body (*dienstcommissie*) was very unhappy with this memo, since interfering with the private lives of employees could have serious consequences for them, especially because 'it seems likely that specifically caretakers have intense contact with pets, either as a hobby or as a side job'.[109] They perceived it as particularly unfair because, according to them, the hygiene measures already taken were far from perfect and much more could be done in that area before advancing to people's private lives. The working group Quality Control of Lab Animals, however, responded by stating that it had been proven that staff taking care of nonhuman animals were the weakest link in the chain of preventive hygiene measures.[110]

ATs became more involved as experts on biotechnical aspects of nonhuman animal experiments and also became more educated from the 1980s onwards.[111] As we saw previously, Laboratory Animal Science had its origins in the 1950s when it focused mostly on efficiency. During the late 1970s and 1980s, it established itself as a discipline in the Netherlands and its scope broadened from efficiency to the 3Rs and included education in ethics as well. One of the earliest national courses on Laboratory Animal Science was organized by the Laboratory Animal Science Federation (*Proefdierkundige Federatie*) at the RIVM during two days in May and June of 1978. The course material contained all kinds of information on how to house and care for different species. It additionally included a section on what the authors called the 'ethical weighing', the ideas of Peter Singer, and the misconceptions among lay people who were described as often having 'a completely mistaken image of the level of our knowledge and the capacity of medical science. People have no idea of the risks they would have to be prepared to take if cer-

107 See Chapter 1 for more on care and instrumentality.

108 Druglitrø, Skilled Care; Beth Greenhough and Emma Roe, 'Attuning to Laboratory Animals and Telling Stories: Learning Animal Geography Research Skills from Animal Technologists', Environment and Planning D: Society and Space, 37.2 (2019), 367–84 <https://doi.org/10.1177/0263775818807720>.

109 Letter from DC-RIVM to the DG RIVM Ir.Drs. R.B.J.C. van Noort, 11/06/86, RIVM Archive, file no. 1016304.

110 Letter from R Boot to Dr R Kroes Re.: Nota 86/86 DC RIVM Houden van Huisdieren, 08/07/86, RIVM Archive, file no. 1016304.

111 L.F.M. Van Zutphen, Proefdieren en Dierproeven (inaugurele rede Rijksuniversiteit Utrecht), 13/11/1985, RIVM Archive, file no. 101402.

tain experiments on animals were to end'.[112] The section continues with a discussion of ethics in relation to those who experiment on nonhuman animals, the ATs:

> In a society like ours, a division of labor is inevitable. Animal experiments also demand knowledge and skills that make it necessary that they are performed by professionals. This aspect of the matter is often overlooked in discussions about animal experimentation. People want to limit animal experiments to those 'strictly necessary' but would be unable to perform even the most necessary ones themselves. Besides the technical side, it also plays a role here that causing pain to another being, or even performing a painless procedure, would be very hard or impossible to do for some people. This does not necessarily mean that these people have a stricter conscience. Sometimes people cannot do it because they themselves cannot endure it. Conversely, it cannot be assumed that the one that does perform animal experiments, has lower ethical norms than other people.[113]

In 1983, Utrecht University established the research group Laboratory Animal Science and appointed Bert van Zutphen to be the first full professor in the discipline.[114] A Laboratory Animal Science course was first held in 1986, meant for everyone who would work with lab animals. It was (and still is) commonly referred to as the 'Article 9 course', because it was Article 9 of the Animal Testing Act that made it compulsory for everyone working in nonhuman animal experimentation. The Netherlands was the first country to make such a course obligatory. The Animal Testing Decree of 1993 set further demands for the education of ATs, although those who started working in nonhuman animal testing before July 2, 1985 were exempted. The annual report on nonhuman animal testing in the Netherlands, *Zodoende*, of 1992 showed an increase in education levels.[115]

The Laboratory Animal Science developments I have discussed so far have focused on two of the three Rs: Refinement and Reduction. Better housing, hygiene, and education were to lead to better science and better welfare for the nonhuman animals being used for testing, as well as to a reduction in nonhuman animal use by preventing intercurrent deaths. However, the last of the 3Rs, Replacement, did become a focus point within the RIVM, the Netherlands, and Europe as well.

The first project on replacement was initiated in 1984 and consisted of a literature study about alternatives in vaccine safety and potency testing. Interestingly, this project was co-funded by seven animal protection organizations and the Dutch government. The 150-page report 'More than routine alone' by RIVM's Coenraad Hendriksen concluded that there were many opportunities to replace and reduce nonhuman animal use.[116] Doing so, however, would require changes to safety regulations and more room for developing innovations.

112 Course binder Introduktiecursus: Proefdieren en Proefdierkunde, 75, RIVM Archive, file no. 2000421499.

113 Course binder Introduktiecursus: Proefdieren en Proefdierkunde, 75, RIVM Archive, file no. 2000421499.

114 L.F.M. Van Zutphen, Proefdieren en Dierproeven (inaugurele rede Rijksuniversiteit Utrecht), 13/11/1985, RIVM Archive, file no. 101402.

115 Veterinaire Hoofdinspectie van de Volksgezondheid, 'Zo Doende 1992, Jaaroverzicht van de Sectie Dierproeven.', 1993.

116 Coenraad Hendriksen, Meer Dan Routine Alleen. Een Literatuurstudie. Mogelijkheden Tot Vervanging, Vermindering En/of Verfijning van Het Proefdiergebruik Bij de Produktie En Controle van Vaccins | RIVM (Rijswijk:

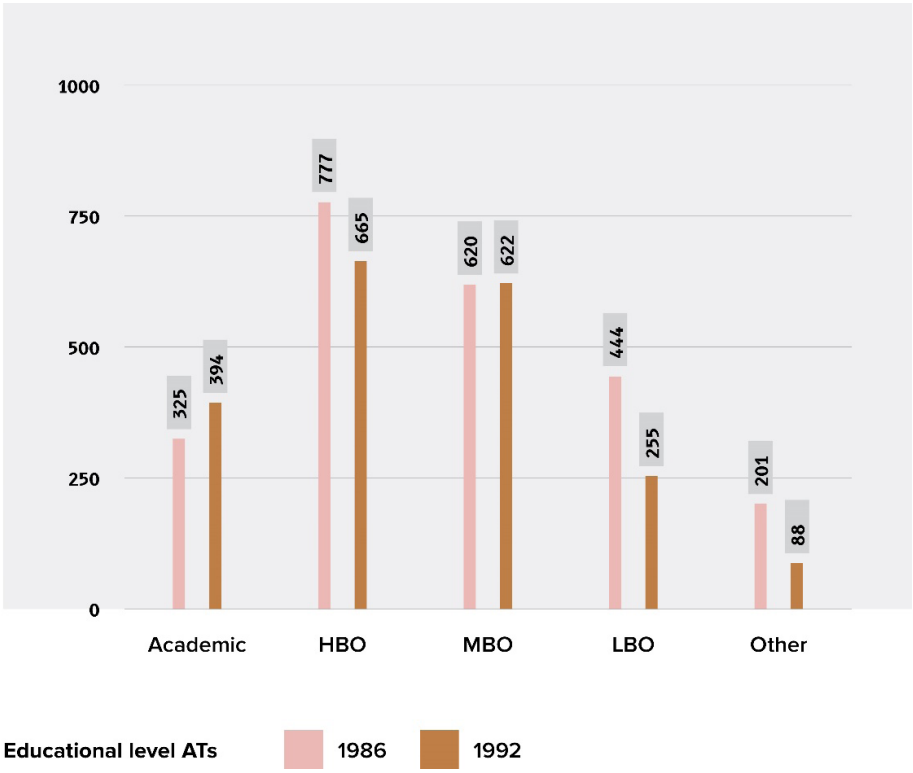

Figure 2.8 Educational level ATs in 1986 and 1992[117]

Several initiatives were taken to stimulate the development of such innovative alternatives. In 1986, the VHI started a working group on alternatives and on August 27, 1987 the government founded the National Platform Alternatives for Animal Testing (PAD in Dutch). PAD had the following tasks: to advise the government on subsidizing alternatives; to take inventory and coordinate and stimulate research on alternatives; and to advise researchers about alternatives. The platform's definition of 'alternatives' reflected the 3Rs: 'research methods that lead to a reduction in the use of research animals as well as minimizing the violation of the wellbeing of lab animals'.[118]

Within the RIVM, the Coordination Point for Alternatives for Animal Testing (CAD in Dutch) was founded in 1991. The main aim of CAD was to 'stimulate and coordinate the implementation of and research about alternatives for nonhuman animal testing within the RIVM'.[119] CAD had a yearly budget of 100,000 guilders and some of its activities were: initiating research into validating or developing alternatives together with researchers; giving out a yearly award within the institute; making an inventory of alternatives being used; sharing information about alternatives via a newsletter; and small scale funding for alternatives projects. As with PAD, alternatives were defined to

Veterinaire Hoofdinspectie van de Volksgezondheid, 1987).

117 Source: ibidem.

118 Letter from State Secretary Dees 'Onderwerp: Instellingsbesluit Platform Alternatieven voor Dierproeven' Rijswijk 27/08/1987, RIVM Archive, file no. 1037565.

119 CAD Beleidsplan 15/10/91 and Conceptbegroting CAD1992, RIVM Archive, file no. 103768.

include all of the 3Rs. The RIVM was the first institute with such a coordination point and was also involved in the creation of the National Coordination Point for Alternatives to Animal Testing (NCAD) in 1992, together with the PAD, TNO, Utrecht University, and Leiden University. To the surprise of the CAD members, its foundation did not go unnoticed in the media, which can perhaps be seen as a sign of increased societal attention to nonhuman animal experimentation (discussed in the next section).[120] An early example of an in vitro alternative that replaced an in vivo test was the ToBI test, which was developed at the RIVM in the late 1980s.[121] RIVM researchers found this in vitro test for measuring tetanus and diphtheria antitoxin in human sera to be not only reliable but also cheaper and quicker than the test using mice.[122]

Figure 2.9 Researcher of vaccine quality Arnoud Akkermans wins the CAD award, 1992. Source: RIVM

The importance of international cooperation and harmonization was recognized, especially on the European level.[123] During the 1990s, several European organizations were created (including ECVAM and ERGATT) and the World Congress on Alternatives for Animal Testing was held for the first time in 1993. The RIVM saw itself as a frontrunner and example for other institutes when it came to their alternatives policy and activities. When, in 1996, the report 'Alternatives Policy' was written by animal advocacy organization Proefdiervrij[124], the RIVM was not impressed since they were already doing all the things suggested in the report.[125] The RIVM generally had a good rela-

120 Jaarverslag CAD 1991, RIVM Archive, file no. 103768 For example: "door A. Kampen Alternatieven voor dierproeven". "Nederlands dagblad: gereformeerd gezinsblad/ hoofdred. P. Jongeling ... [et al.]". Amersfoort, 1992/01/13 00:00:00, p. 11. Visited on Delpher on 04-03-2021, http://resolver.kb.nl/resolve?urn=ddd:010559866:mpeg21:p011.

121 C. F. M. Hendriksen, J. W. van der Gun, and J. G. Kreeftenberg, 'Combined Estimation of Tetanus and Diphtheria Antitoxin in Human Sera by the in Vitro Toxin-Binding Inhibition (ToBI) Test', Journal of Biological Standardization, 17.2 (1989), 191–200 <https://doi.org/10.1016/0092-1157(89)90009-7>.

122 C.F.M. Hendriksen, 'Alternatieven Voor Dierproeven', Nederlands Tijdschrift Voor Geneeskunde, 135 (1991), 1896–1900.

123 Interview R1.

124 In 1994, NBBV changed its name to Proefdiervrij.

125 Letter to Bob Kroes about Nota Alternatievenbeleid Proefdiervrij, 22/11/1995, RIVM Archive, file no.

tionship with the NBBV, the oldest and biggest lab animal advocacy organization, and maintained this positive relationship even throughout the significant changes in the societal and political climate regarding nonhuman animal testing over the course of the 1980s and 1990s.

2.4.4 Society

> The issue of animal experimentation is close to my heart. I think about it the same way as I think about excessive meat consumption. I am also not really in favor of that, as people have been able to read these days. I think that animal experiments should be stopped as much as possible and, if at all possible, abolished. There are developments going on in this regard. The RIV for instance pays a lot of attention to this. I cannot say more than I have already said just now. Mister Toussaint has asked for a policy brief on this issue. The Parliament will get this. That is how important the subject is to me. Let the Parliament not make me commit to a time period. I need to take the time for this.[126]

Figure 2.10 Van der Reijden wins prize 'animal protector of the year', 1984. Source: Rob Bogaerts / Anefo, Nationaal Archief

The above is a quote from State Secretary Van der Reijden in 1983, who won the prize 'animal protector of the year' in 1984. He made this statement in response to questions 1019471.

126 Handelingen II (1983-1984), 28, 01/12/1983, 1652. Available online at: https://repository.overheid.nl/frbr/sgd/19831984/0000132294/1/pdf/SGD_19831984_0000657.pdf.

from members of Parliament asking for a policy report on nonhuman animal experimentation and expressing concern about the lack of inspectors checking compliance with the new law. Van Der Reijden's statement of caring about and wanting to end nonhuman animal testing as well as his comment on meat consumption are exemplary of the renewed political and societal interest in the subject of human-nonhuman animal relations from the late 1970s onwards.

The increased attention to lab animal welfare described earlier is understandable in light of how human perspectives on other animals had changed. In the 1950s, it was assumed that nonhuman animal behavior could be explained as responses to basic drives such as hunger or pain. Later research showed that nonhuman animals are much more complex.[127] Research on nonhuman animal cognition has resulted in understandings of a "sharp divide" between human and nonhuman animals fading out.[128] Psychological research using primates was particularly influential in changing many people's views and led to stronger opposition to the use of non-human primates in research as people realized how similar non-human primates are to humans.[129] These experiments made the paradox of human-nonhuman animal relations in nonhuman animal testing very clear: nonhuman animals have to be both similar enough as well as dissimilar enough to human animals in order to justify their use in experimentation. Of course, lab animals are only a small percentage of nonhumans used by humans. Human-nonhuman animal relations in general can easily be described as paradoxical as well. This paradox intensified in the 20th century but has a long history, as described by Keith Thomas for the period 1500–1800:

> Economic independence of animal power and urban isolation from animal farming had nourished emotional attitudes which were hard, if not impossible, to reconcile with the exploitation of animals by which most people lived. Henceforth an increasingly sentimental view of animals as pets and objects of contemplation would jostle uneasily alongside the harsh facts of a world in which the elimination of 'pests' and the breeding of animals for slaughter grew everyday more efficient.[130]

This paradox is also visible in the legislative documents dealing with nonhuman animals that on the one hand aimed to protect them but on the other hand made nonhuman animals into objects and property. While in the 1960s and 1970s the focus within policy was mostly on nonhuman animal welfare, in the 1980s the concept of "intrinsic value" entered the discussion and also made its way into the policy note 'Government and Animal Protection' of 1981.[131] In the note, intrinsic value was understood to mean that nonhuman animals have value in and of themselves, separate from their instrumental value for humans. Although the note states that the intrinsic value of nonhuman

127 The Inevitable Bond: Examining Scientist-Animal Interactions, ed. by Hank Davis and Dianne Balfour (Cambridge [etc.]: Cambridge U.P, 1992).

128 Lynda Birke, Mette Bryld, and Nina Lykke, 'Animal Performances', Feminist Theory, 5.2 (2004), 167–83 <https://doi.org/10.1177/1464700104045406>.

129 Guerrini, Experimenting with.

130 Keith Thomas, Man and the Natural World: Changing Attitudes in England 1500-1800 (New York, 1996), 301.

131 Nota Rijksoverheid en Dierenbescherming, 1981 CRM.

animals (as well as 'nature' in general) is a central tenet of animal and nature protection laws, they also conclude that in practice intrinsic value is a difficult concept:

> The choice for the intrinsic value of the individual animal as point of departure [for legislation] has as its consequence, that the function of the animal for the human (economic utility, educational or entertainment function, et cetera) can be subordinated or has to be weighed against it. This weighing – as regulations and practice teach us – is a perilous endeavor. Within our Western cultural patterns, an anthropocentric interpretation in which the animal is the weaker party, can hardly be avoided.[132]

This difficulty of reconciling the recognition of the intrinsic value of nonhuman animals with using them as research objects became especially apparent in discussions about Animal Experiments Committees and the ethical reviews they were supposed to perform (see Chapter 4 for a detailed discussion).

During the (late) 1970s and 1980s, animal activism moved back into the public picture, this time with a strong focus on nonhuman animal rights (drawing on analogies with human rights activism). The animal rights movement became well organized and strongly founded in ethical principles.[133] Important philosophical works were published on the subject, perhaps most famously *Animal Liberation* by Peter Singer in 1975.[134] Animal rights activism also became more coordinated and more strategically targeted in certain cases, managing to create a substantial impact on public debate. A good example of this is an advertisement in the New York Times by Henry Spira in 1980 condemning the use of rabbits by Revlon for painful eye-irritation tests (the Draize test), which caused public outrage and eventually led to Revlon making money available for researching alternatives.[135] The period also saw some newly founded activist groups (such as the Animal Liberation Front (ALF) founded in 1976) resorting to illegal forms of direct action such as destruction of laboratories, mostly in the US and UK.[136] Yet a large majority of people remained supportive of nonhuman animal testing (at least for medical purposes).[137] In 1983, the NBBV commissioned the Dutch Institute for Public Opinion (NIPO) to investigate public attitudes towards nonhuman animal experimentation. Their questionnaire gave the following results: 18% of respondents had serious objections with using nonhuman animal experiments for medical purposes, 16% had no objections, and 64% had some objections but thought the experiments needed to be done anyway.[138] For experiments in cosmetic testing, the numbers were very different:

132 Nota Rijksoverheid en Dierenbescherming, 1981 CRM, 13.

133 Rowan, Of Mice.

134 Peter Singer, Animal Liberation: The Definitive Classic of the Animal Movement, Updated ed. edition (New York: Harper Perennial Modern Classics, 2009).

135 Rowan, Of Mice.

136 Best Ph D. Steven and Nocella II J Anthony, The Animal Liberation Front: A Political and Philosophical Analysis (Lantern Books, 2011).

137 For a review of research on public attitudes towards animal research, see: Elisabeth H. Ormandy and Catherine A. Schuppli, 'Public Attitudes toward Animal Research: A Review', Animals, 4.3 (2014), 391–408 <https://doi.org/10.3390/ani4030391>.

138 Tweede Kamer Stukken (1984-1985), Dierproevenbeleid; Lijst van antwoorden, 26/02/1985, 18 450, nr.4, 11.

81%, 13%, and 4%, respectively.[139]

In the Netherlands, animal advocacy organizations NVBD[140] and NBBV regularly joined forces and employed a variety of (non-violent) strategies to advocate for tested animals. One commonly used tactic was to write "black books" of nonhuman animal laboratories and breeding centers. A common response by scientists to such negative press was to employ a discursive strategy disqualifying activists as 'too emotional'.[141] In 1985, for example, Director General of the RIVM Hans Cohen wrote a letter in response to an article on reducing nonhuman animal testing in the Dutch newspaper NRC. In this letter he stated:

> Reducing the number of animals used should be the outcome of a rational approach of the problem and if this were to happen on the basis of emotional responses instead, it would lead to ending or limiting of the national vaccination program, with all due consequences.[142]

Other strategies which Dutch animal advocacy groups used included public protest, writing letters, writing reports, and cooperation in developing alternatives.[143] They often adopted the language of the 3Rs discourse and emphasized how using alternatives would lead to "better science", thereby positioning themselves in alignment with rather than in opposition to scientists. This was recognized among scientists, leading Hendriksen to state during a staff meeting in 1987 that:

> Usually, the relation between animal protectors and scientist internationally is not optimal, but in the Netherlands this is different. Most of the animal protection organization - and this should be said as well sometimes - do not take a dogmatic, but a constructive and cooperative stance.[144]

In the same year, Henk Smid of the NBBV wrote an article in the journal *Medisch Contact* entitled 'Stagnating Animal Testing Policy'. In the article, he evaluated ten years of dialogue between animal protection organizations, researchers, and government. He concluded that animal protection organizations had shown themselves willing to enter into dialogue: they published the book *Animal Experiments in Modern Society* and organized the symposium 'Thinking about the limits of the permissibility of animal experiments'.[145] Their goal was to jointly strive for improving the situation of lab animals.

139 Ibidem.

140 Nederlandse Vereniging tot Bescherming van Dieren; translated: Dutch Society for the Protection of Animals.

141 Mike Michael en Lynda Birke, 'Accounting for Animal Experiments: Identity and Disreputable "Others"', Science, Technology, & Human Values, 19 (1994) 189–204. See also: Anne van Veen, 'De Muis van Troje', Ex Tempore, 37.3 (2018), 244–57.

142 Letter from DG H. Cohen about 'Vermindering van dierproeven in NRC (Wiegant, De Wied, Henk Smid)', 04/04/1985, RIVM Archive, file no. 12092.

143 For a more elaborate discussion of two instances of protest against animal testing in the Netherlands, see: Van Veen, De Muis van Troje.

144 Verslag 213e wetenschappelijke vergadering 'Alternatieven voor Dierproeven', 29/01/1987, RIVM Archive, file no. 1025667.

145 Henk Smid, 'Stagnerend Dierproevenbeleid', Medisch Contact, 40 (02/10/1987), 1261-1263.

However, after ten years he could only conclude that '[...] government and researchers have fallen short in the execution of the animal testing policy. In animal protection circles, there is great disappointment about this'.[146] He stated that while the government had rhetorically been a strong proponent of nonhuman animal testing policies in their speeches and writing, they had not lived up to this in practice and had failed to take action. He argued that researchers had also been too passive in implementing the 3Rs. Based on this, Smid was concerned that the dialogue would end in an impasse, which he feared would lead to a situation similar to the on in the UK where the ALF responded to the Research Defense Society with violence. 'It would be disastrous when this situation would also emerge in our country'.[147] Instead, he pleaded with the government and researchers to develop a joint vision with animal protection organizations, including an action program and adequate financing. This would require compromises from all stakeholders, he claimed, including from animal protection organizations, who would have to put pragmatism above ideology.

Summary

In the changing societal environment, nonhuman animal experimentation and alternative practices needed to change as well. Society and politicians demanded that scientists show more accountability by dealing more explicitly with ethical questions. A solution was found in the creation of (more) legislation recognizing the intrinsic value of nonhuman animals and the establishment of AECs, which can be seen as a compromise between the demands of scientists, society, and politicians. Within Laboratory Animal Science, we saw that the 3Rs became popular and expanded the definition of alternatives to include refinement and reduction. The focus on hygiene and nonhuman animal welfare intensified, meaning increased control over various aspects of the lives of nonhuman animals (e.g., when breeding programs replaced catching wild animals). The focus on welfare became about more than ensuring high quality research results, it also became a matter of moral duty towards nonhuman animals and 'ethics' and 'intrinsic value' became important terms in discussions on nonhuman animal experimentation. Importantly, nonhuman animals remained objects within this discourse, limiting the meaning of care and ethics to what was practicable within the context of nonhuman animal experimentation (i.e., the moral duty to care and recognize the intrinsic value of other animals was only translated into practice in ways that did not obstruct those nonhuman animal experiments deemed necessary by humans).

2.5 THE DISCOURSE OF BETTER SCIENCE CONTINUES: PROLIFERATION OF THE 3RS AND NON-ANIMAL INNOVATIONS (1998–2020)

2.5.1 The Nonhuman Animals

On the national level, the period after 1997 started with a small increase in the use of nonhuman animals, followed by a small decrease, and remained stable afterwards. The 17.9% increase in experiments registered in 2014 seems to have been caused by a switch to the EU system of registration that became mandatory that year. In the EU registration system, second generation offspring of genetically modified animal strains

146 Ibidem, 1262.

147 Ibidem, 1263.

were also counted as experimental animals, unless it could be shown in a welfare evaluation that they did not suffer.[148]

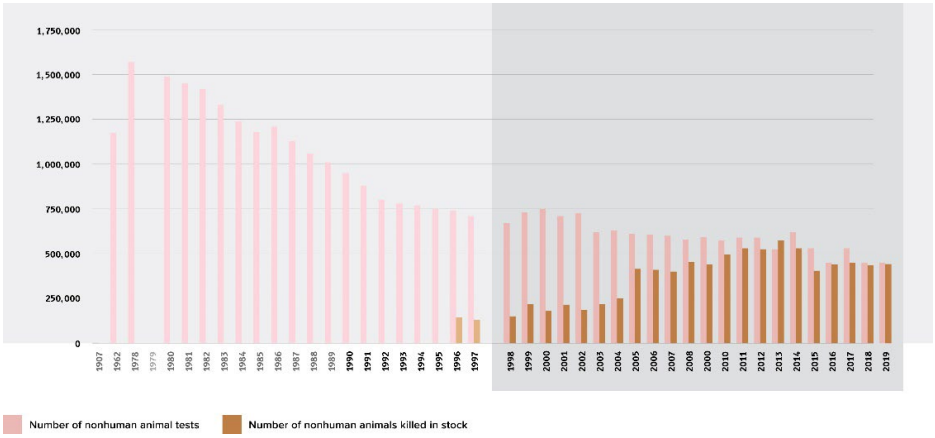

Figure 2.11 Number of nonhuman animal tests and nonhuman animals killed in stock in the Netherlands 1907-2019: 1998-2019[149]

There were also nonhuman animals who were not counted as tested animals by the EU but who were counted in the Dutch registration system. These were nonhuman animals who were not experimented on when alive, but who were killed for the use of their organs, tissues, or bodily fluids. There have also been many other animals who have been killed in nonhuman animal experimentation practices, but who have not been counted as experimental animals. As mentioned before, invertebrates are not counted as "animals" within the context of animal testing laws, with the exception of cephalopods who were added after 2013 to the animal species counted in the Directive 2010/63/EU 'Protection of Animals used for Scientific Purposes'.[150] Vertebrate nonhuman animals who have been registered but not counted as experimental animals are so-called 'animals killed in stock'. They were born in breeding programs for scientific research and killed but were not used in experiments, often because they had the wrong genotype or gender. With the rise of transgenic techniques, the number of animals killed in stock also began to rise (see also Chapters 5 and 6), as can be seen in the figure below:

148 Ministerie van Algemene Zaken, 'Jaarverslag NVWA "Zo doende 2014" - Jaarverslag - Rijksoverheid.nl' (Ministerie van Algemene Zaken, 2016).

149 Sources: Kluveld-Reijerse, Reis door de Hel; Tweede Kamer Stukken, verslag 19e vergadering 1964-1965 (15/12/1964), 768; Veterinaire Hoofdinspectie van de Volksgezondheid. Sectie Dierproeven and Nederlandse Voedsel- en Warenautoriteit., 'Zo doende ...: jaaroverzicht door de Sectie Dierproeven van de Veterinaire Hoofdinspectie van de Volksgezondheid over het jaar ...', series 1978-2021.

150 Graziano Fiorito and others, 'Cephalopods in Neuroscience: Regulations, Research and the 3Rs', Invertebrate Neuroscience, 14.1 (2014), 13–36.

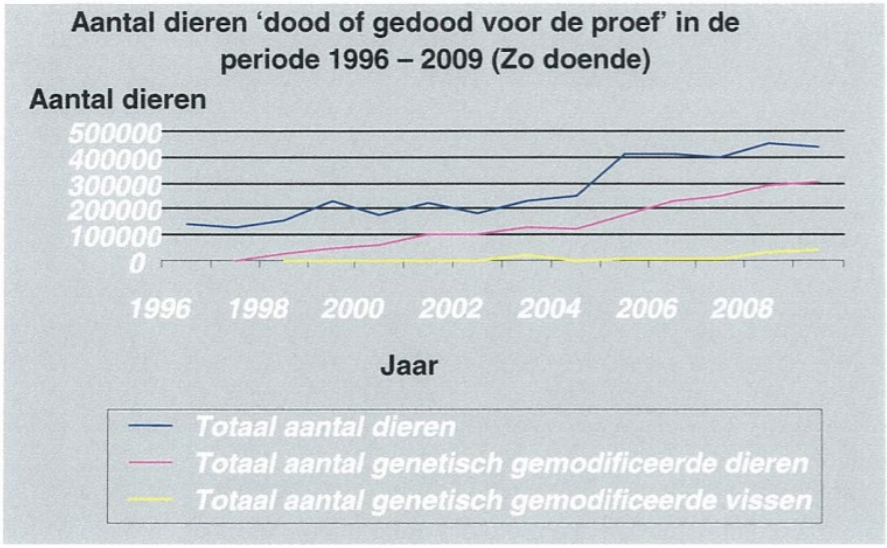

Figure 2.12 'Number of animals 'dead or killed before the experiment' in the period 1996–2009 (Zo doende)'[151]

This was reason for Parliament to ask questions about the matter of 'animals killed in stock'; Minister Ab Klink of Public Health, Welfare, and Sport in turn asked the CCD[152] to write a recommendation on the causes of the rising numbers and potential solutions. In their recommendation, the CCD suggested improving breeding management by centralizing breeding at the institutional level as a way of improving efficiency. This would not only reduce nonhuman animals killed in stock but also costs.[153] In the years that followed, however, the number would only increase (see Figure 2.11). In 2013, more nonhuman animals were killed in stock than were used in experiments. Of the 574,511 nonhuman animals killed in stock, 446,026 were genetically modified animals, mostly mice (303,299) and fish (140,941).[154] To compare, 450,689 nonhuman animals (of which 217,256 were mice) were used in experiments in the same year.[155] The State Secretary of Economic Affairs requested another recommendation, this time from the National Committee on Advice for Animal Experimentation Policies (NCad). The Committee published their report in 2015, advising that both quality criteria and efficiency criteria be implemented (e.g., establishing centers of excellence and appointing breeding coordinators, using both genders, a critical review by the CCD), but also stating

151 Source: Appendix to letter from Coenraad Hendriksen (Chair CCD) to Minister E.I. Schippers of VWS. Verzoek advies "dieren in voorraad gedood". 23/11/2010.

152 The CvAvdD had changed its name to CCD.

153 Letter from Coenraad Hendriksen (Chair CCD) to Minister E.I. Schippers of VWS. Verzoek advies "dieren in voorraad gedood". 23/11/2010.

154 Ministerie van Algemene Zaken, 'Jaarverslag NVWA "Zo doende 2013" - Jaarverslag - Rijksoverheid.nl' (Ministerie van Algemene Zaken, 2014).

155 Ibidem.

that: 'The NCad, therefore, believes that if the problems associated with the breeding of genetically modified animals are to be solved, then a comprehensive approach aimed at a net reduction in laboratory animals will be required'.[156]

Over the years, mice have remained the most "popular" (counted) research animals, followed by rats. Fish, especially zebrafish, have also become increasingly popular during this period.[157] Great apes in contrast were never a popular species for research purposes in the Netherlands and their use became illegal in 2002.[158]

Looking at the nonhuman animals used within the RIVM during this period, we can see both differences and similarities when compared to national developments in nonhuman animal use. Within the RIVM there was also a small increase in nonhuman animal use in the late 1990s yet, unlike on the national level, this was followed by a sharp reduction in the number of nonhuman animals used. According to the 2008 annual report from the RIVM Advisory Group on Lab Animal Policy, the reduction before 2009 was a consequence of a change of tasks (e.g., moving vaccine-related testing to the Netherlands Vaccine Institute, (NVI)), reduction of funds, reluctance to experiment on nonhuman animals, and strategic choices.[159] On paper, the RIVM completely stopped experimenting on nonhuman animals when they became a client of the Animal Research Center of the NVI in 2009 instead of co-administrator.[160] Since then, RIVM is no longer a license holder and therefore no longer registers nonhuman animal experiments.[161] Even if we include the numbers of the NVI, there was still a stronger reduction in nonhuman animal use compared to the national trend (see Figure 2.3). Alternatives did play a role in the reduction of nonhuman animals used in vaccine research, the main focus of the NVI.[162]

Transgenic animals became popular within the RIVM/NVI as well, mostly in the 1990s, but there was also a spike in their use in 2008.[163] More recently, the use of transgenic animals has declined and there are no longer many transgenic mouse strains being bred in Bilthoven (see Chapters 5 and 6). One remaining mouse strain is a strain in which the mice have been modified to be receptive to the poliovirus (see Chapter 3).

While in the 1960s the RIVM was the institute using most of the nonhuman primates who were experimented upon in the Netherlands, the use of primates had ended com-

156 NCad, Genetisch gemodificeerde dieren in voorraad gedood (Den Haag, 2015), 5.

157 Courtney Graham, Marina A. G. von Keyserlingk, and Becca Franks, 'Zebrafish Welfare: Natural History, Social Motivation and Behaviour', Applied Animal Behaviour Science, 200 (2018), 13–22 <https://doi.org/10.1016/j.applanim.2017.11.005>.

158 Tweede Kamer Stukken (2002-2003), 28503 'Wijziging van de Wet op de dierproeven, nr. 4, 06/11/2002, 4. Available online at https://zoek.officielebekendmakingen.nl/kst-28503-4.html.

159 Jaarverslag Adviesgroep Proefdierbeleid 2008, RIVM Archive, file no. 1215.

160 See figure I.2 on for a schematic of how nonhuman animal experimentation facilities moved between the RIVM and other organizations.

161 Although they are no a longer license holder, the RIVM has remained involved in nonhuman experimentation. These experiments are now contracted out to the Animal Research Center, which was part of the NVI and became part of Intravacc when NVI merged with the vaccine department of the RIVM to became Intravacc in 2013. In 2019, the ARC became part of Poonwalla Science Park, the owner of Utrecht Science Park/Bilthoven where RIVM is currently located. The RIVM is about to move to Utrecht Science Park/Utrecht and it remains unclear what will happen regarding research using nonhuman animal experimentation. It could be the case that they become a license holder again.

162 NVI jaarverslag 2007 functionaris EX Art 14 Wod NVI, 14, RIVM Archive, file no. 1215.

163 Jaarverslag Art. 14 functionaris 2008.

pletely by the late 2000s (see Chapter 3). The same holds for many other species, narrowing the variety of nonhuman animals being used to mice, rats, fish, and sometimes ferrets.[164]

2.5.2 Law

From 1996 onwards, license holders had to comply with the revised Animal Testing Act, which was stricter than the previous act in several ways. With this new legislation, responsibility for deciding on the permissibility of experiments shifted from individual researchers to Animal Experiments Committees.[165] The 2010 EU directive on 'The protection of animals used for scientific purposes' mandated the establishment of national committees, shifting the responsibility from Animal Experiments Committees to the Central Committee Animal Experimentation (*CCD* in Dutch).[166] Although this national committee has been given final responsibility in reviewing the permissibility of experiments, AECs have continued their work of reviewing experiments, but now give their advice to the CCD rather than to the license holder.[167]

Additionally, during this period new legislation was created which regulated specific experiments and/or experimental animals. The law of 1996 banned testing for cosmetic products as well as the painful LC/LD50 tests (unless no alternative was available).[168] Testing cosmetic products was forbidden in the entire EU in 2004 and, since 2009, separate ingredients of cosmetic products cannot be tested on nonhuman animals either. Selling cosmetics products in the EU that have been tested on nonhuman animals elsewhere likewise became forbidden in 2013. The use of great apes in experiments was forbidden in 2002 in the EU. Cephalopods on the other hand gained legal recognition as nonhuman animals that can suffer and that should therefore be subject to nonhuman animal testing regulations.

2.5.3 Laboratory Animal Science

In the Netherlands and internationally, the 3Rs continued to be the dominant discourse within Laboratory Animal Science and government policy.[169] There were however significant shifts within this discourse. A discourse analysis by Pijnappel reveals an increasing 'technology push' approach in which 'alternatives' are seen as the solution to the problem of nonhuman animal experimentation.[170] Policy documents no longer focused on the trade-off between nonhuman animal protection and science but on the win-win situation in which scientifically superior alternatives to nonhuman animal

164 Oral communication when I visited the Intravacc Animal Research Center on 19/05/2017.

165 Pijnappel, Lost in Technification.

166 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 Text with EEA Relevance, 276, 2010, OJ L <http://data.europa.eu/eli/dir/2010/63/oj/eng> [accessed 4 March 2021].

167 For the current procedure, see: Natuur en Voedselkwaliteit Ministerie van Landbouw, 'Centrale Commissie Dierproeven - Centrale Commissie Dierproeven' (Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2017) <https://www.centralecommissiedierproeven.nl/>.

168 Welzijn en Sport Ministerie van Volksgezondheid, 'Wet van 12 september 1996 tot wijziging van de Wet op de dierproeven' (Ministerie van Justitie, 1996).

169 For the Netherlands: Tweede Kamer Stukken (2007-2008) Kabinetsvisie "Alternatieven voor Dierproeven" (30 168, nr. 4), 04/06/2008. Internationally: Tannenbaum & Bennet, Russel and Burch's 3Rs.

170 Pijnappel, Lost in Technification.

testing reduce the number of nonhuman animals used in experiments.

The meaning of 'alternatives' has expanded even further to not only include one-to-one replacements (besides refinement and reduction), but also in vitro methods that are part of a chain-approach and in that way reduce nonhuman animal experimentation without replacing any specific experiment. An example of this are in vitro pre-screening tests, which weed out substances that do not stand a chance of passing the nonhuman animal test, thereby reducing the number of substances that are tested on nonhuman animals.[171]

Another shift within the 3Rs discourse was from separate alternative development projects towards (internationally) coordinated development, validation, and implementation.[172] To coordinate national policy, the Interdepartmental Steering Group and Working Group Alternatives for Animal Testing was created in 2008. In 2010, the Dutch government established the National Knowledge Center for Alternatives to Animal Testing (NKCA*)* with the aim to nationally coordinate the development and knowledge of alternatives and to advise the government on alternatives policy. The center was run by the RIVM and Utrecht University and was a continuation of the NCA but with expanded responsibilities. In 2014, the NKCA closed and in its stead the NCad was established, taking over some of NKCA's activities. NCad was created to comply with the 2010 EU directive which obliged each member state to have a national committee which advises on nonhuman animal testing.[173] The mission of the NCad was, as expected, centered around the 3Rs. According to NCad's website, its aim is to:

> […] protect animals that are being used in science and education. The NCad realises visible improvements aimed at Replacing, Reducing and Refining (3Rs) of animal experiments and the ethical review thereof in (applied) scientific research and education to minimize the use of experimental animals both nationally and internationally.[174]

In December 2016, State Secretary Van Dam stated that the Netherlands should be a world leader in animal-free innovations by 2025.[175] He made this statement when he received the NCad report 'Transitions Towards Animal-Free Research', which he had commissioned in March 2016 asking NCad to draw up a schedule for phasing out experiments on nonhuman animals.[176] This advice led to the establishment of the Transition Program for Innovation Without the Use of Animals (TPI), which aims to accelerate the development of animal-free innovation. TPI focuses not so much on developing these innovations themselves, but on stimulating the transition and connecting stakeholders.

171 Pijnappel, Lost in Technification, 198; Interview R1.

172 Tweede Kamer Stukken (2007-2008) Kabinetsvisie "Alternatieven voor Dierproeven" (30 168, nr. 4), 04/06/2008.

173 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 Text with EEA Relevance, 276, 2010, OJ L <http://data.europa.eu/eli/dir/2010/63/oj/eng> [accessed 4 March 2021].

174 Natuur en Voedselkwaliteit Ministerie van Landbouw, 'Home - Nationaal Comité advies dierproevenbeleid' (Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2017) <https://www.ncadierproevenbeleid.nl/>.

175 'Van Dam: In 2025 meeste dierproeven vervangen door innovatief onderzoek', TGTHR.nl <https://tgthr.nl/nieuws-van-leden/van-dam-in-2025-meeste-dierproeven-vervangen-door-innovatief-onderzoek/>.

176 NCad, Transitie naar proefdiervrij onderzoek (Den Haag, December 2016).

The core members of TPI come from the government, governmental agencies (including RIVM), academia, businesses, and society (including Proefdiervrij). Currently, in 2021, Anne Kienhuis is the project coordinator for the 3Rs at the RIVM and is involved in the TPI program. In an interview, she explained the vision they have developed on how the 3Rs and TPI relate to one another, as illustrated in Figure 2.13:

> At RIVM, we invest in 3Rs. For the ministry of LNV, and in the context of TPI, we do this in relation to regulations for the safety assessment of chemicals. According to the current 3Rs policy, we work towards reducing animal testing, by accelerating the process from development towards implementation of 3Rs methods in safety testing. We call this evolution. This we have been doing traditionally and continue to do. In parallel, also in the context of TPI, we strongly focus on experimentation, where we investigate emerging concepts and the integration of innovative technologies for the application in safety assessment. This is currently a conceptual approach which we call "revolution". In this approach we move away from the animal test as the gold standard towards human biology instead, we call this "revolution".[177]

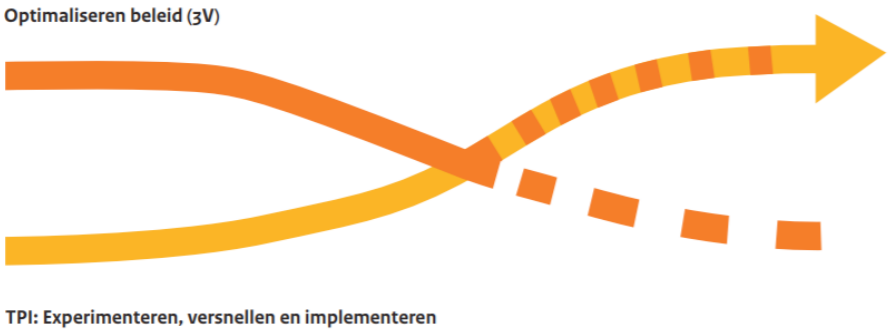

Figure 2.13 Optimizing policy (3Rs) and TPI: Accelerating, experimenting and implementing[178]

In 2018, the Ministry of Agriculture, Nature and Food Quality (*LNV*) adjusted its ambition. They no longer wanted to be world leader in animal-free innovation by 2025, but front runner—among the top ten, but not necessarily number one. Additionally, the core group of TPI decided to let go of 2025 as a target year.[179] On the TPI website they state: 'We are facing huge, pervasive transitions that often come at a considerable cost in terms of both time and money. Some of them require changes to international rules. As a result, it can be hard to predict when laboratory animals will hardly or no longer

177 Interview Kienhuis.

178 Ministerie van Algemene Zaken, 'Transitie Proefdiervrije Innovatie: filosofie en werkwijze - Rapport - Rijksoverheid.nl' (Ministerie van Algemene Zaken, 2018) <https://www.rijksoverheid.nl/documenten/rapporten/2018/06/01/transitie-proefdiervrije-innovatie>, 5.

179 Leane van Weereld (2018). Verslag. Zevenendertigste bijeenkomst Nationaal Comité advies dierproevenbeleid. D.d. 18-05-2018

be required anymore'.[180] According to Kienhuis, work regarding the safety assessment of chemicals and pharmaceuticals, towards "revolution" and human biology as the new standard, is conceptual at the moment and still in its beginning stages. When this crossing point of evolution and revolution depicted in Figure 2.13 will be reached is impossible to predict given the number of factors involved.

In the previous sections we saw how the RIVM positioned itself as an (inter)national expert in Laboratory Animal Science and the 3Rs. During this period, RIVM's responsibilities changed and consequently involved a lot less nonhuman animal experimentation. In 2009 they stopped being license holders and became clients of the Animal Research Centre instead. These developments made it impossible for the RIVM to maintain their position as Laboratory Animal Science experts, the 'critical mass' was simply lacking.[181] R1, member of the Advice Group Lab Animal Policy, created in 2004, spoke of the 'old' and 'new' RIVM.[182] The old RIVM was known for its high-quality lab animal facility and had vaccine control as one of its major tasks. With respect to the 3Rs, the focus was on developing in vitro technologies that replaced or reduced nonhuman animal testing, as well as on refinement. R1 mentioned the work on humane endpoints as a typical example from the 'old' RIVM. Humane endpoints can be defined as:

> […] the earliest indicator in an animal experiment of (potential) *pain* and/or *distress* that, within the context of moral justification and scientific endpoints to be met, can be used to avoid or limit pain and/or distress by taking actions such as humane killing or terminating or alleviating the pain and distress.[183]

With the vaccine work moving away from the RIVM, so did much of the nonhuman animal experimentation. The institute had to cultivate expertise elsewhere if they wanted to maintain their position as international experts. Their focus mostly shifted from developing alternatives towards policy creation, validation, and implementation. An exception is the research of Aldert Piersma and his colleagues, co-financed by Proefdiervrij, which focuses on reducing the use of nonhuman animals in Reproductive Toxicology.[184]

Additionally, within the RIVM there are voices advocating for a move away from the nonhuman animal experiment as the starting point and 'golden standard' for developing non-animal research methods. According to R1, we should focus on Replacement and use the term innovations instead of alternatives, especially if we want to convince

180 Natuur en Voedselkwaliteit Ministerie van Landbouw, 'The TPI's Aim - English - Transitie Proefdiervrije Innovatie' (Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2018) <https://www.transitieproefdiervrijeinnovatie.nl/english/tpi%E2%80%99s-aim>.

181 Kort verslag vergadering Adviesgroep Proefdierbeleid, 02/10/2008, RIVM Archive, file no. 1215; Jaarverslag Adviesgroep Proefdierbeleid 2008, RIVM Archive, file no. 1215.

182 Interview R1.

183 Coenraad F.M. Hendriksen and David B. Morton (editors), Humane Endpoints in Animal Experiments for Biomedical Research — Proceedings of the International Conference, 22-25 November 1998, Zeist, The Netherlands, The Royal Society of Medicine Press Limited, United Kingdom, 1999

184 For example: Victoria C. de Leeuw and others, 'Differential Effects of Fluoxetine and Venlafaxine in the Neural Embryonic Stem Cell Test (ESTn) Revealed by a Cell Lineage Map', NeuroToxicology, 76 (2020), 1–9 <https://doi.org/10.1016/j.neuro.2019.09.014>. See also: 'Prof. Dr. A.H. (Aldert) Piersma | RIVM' <https://www.rivm.nl/rivm/kennis-en-kunde/experts-en-expertise/prof-dr-a-h-aldert-piersma>.

other scientists on an international level.[185] He explained that whereas an animal test is 'blind', in vitro tests are much more precise and provide much more information, making them of better quality than animal tests. He thinks that this improvement in quality has more potential to be convincing than concerns for nonhuman animal welfare:

> I was at an international Asian workshop, [...], to explain it to people in the region there. In that region many vaccine production locations are created and there they work a lot with lab animals and you do not convince them with animal welfare, but with how you can do it differently, smarter. [...] There really is also a lot to gain there regarding the 3Rs, but you have the term leapfrogging, and I wish they would be able to skip the 3Rs phase and go immediately to the more innovative tests. [...] So I think that we should frame it as an innovative opportunity. Because if you develop a new test now with in vitro (methods) and characterize it well from the beginning, you do not need the animal studies, great opportunity.[186]

For Anne Kienhuis the focus on scientific progress and more human-relevant safety assessments is more promising than a focus on nonhuman animal welfare when it comes to engaging other stakeholders, such as scientists and regulators, in the revolution for safety assessment:

> Yes, better science is really the argument that we often use [...] What we often say is "Safety, 'by the way' achieved without animal testing", with safety as the primary goal in safety assessment. With, of course, focus on animal welfare as well.[187]

Kienhuis sees focusing on *moving towards* better science and improved, human relevant, safety assessments not only as more motivating but also as more inclusive: '[...] because if you (only) focus on ethics and *moving away from* animal testing, you get a different discussion, one that I feel is less constructive.' In this sense, "better science" in this discourse is focused on scientific progress (specifically science which is more relevant to human biology and physiology) not on science that is ethically better because it no longer uses nonhuman animals. Next, we will see if this "better science" discourse is also working to avoid discussion in society at large.

2.5.4 Society

> The Dutch citizen asks for safe, affordable and available treatments, medication and consumer products, that have also been created or brought onto the market in a way that is ethically sound. With the current state of affairs in science, it is impossible to completely comply with all these different demands. Time and again, we have to weigh the desires for taking into account animal welfare as much as possible, the wish for progress in

185 Interview R1.

186 Interview R1.

187 Interview Kienhuis.

> innovative scientific developments, strengthening the economic position, and conserving consumer safety.[188]

This quote is from the 2008 government vision on alternatives. While it still uses the language of a trade-off, two sentences later, the switch is made to a discourse of "win-win"—'The key to this is optimally seizing the opportunities and possibilities to develop and actually implement more 3R alternatives'—which would make it possible to produce consumer products safely as well as ethically.[189] This switch in discourse within alternatives policy was already discussed in the previous section. Next, we will take a look at how society in general and activists in particular thought about nonhuman animal testing and the 3Rs during this period. In the previous period, we saw that animal activism became more prominent in the Netherlands and that while most activists took a cooperative position, there were also disappointment (as expressed by Smid) and worry on the part of activists and government that a lack of progress in reducing nonhuman animal testing would lead to radicalization, as was happening in the UK.[190]

Reports by the Dutch General Intelligence and Security Service (AIVD) show that from the mid-1980s, there has indeed been an increase in illegal action by animal activists, namely by a small minority of activists influenced by colleagues in other countries (mostly ALF in the UK). By the late 1990s, these illegal actions still happened occasionally (again only by a small minority) but were mostly uncoordinated and done by individuals or very small "organizations".[191] Since 2009, there has been a reduction in the number of 'actions, extremist and the use of violence', according to the AIVD. Certain groups have also shifted to more peaceful means of protest.[192] The May 2020 report 'Overview of Terrorist Threats in the Netherlands: Radicalization, Extremism, Terrorism,' by the National Coordinator for Security and Counterterrorism (NCTV) devotes just two sentences to animal activism, concluding that: 'The Dutch animal rights movement, however, has been small for a long time and expresses itself mostly through peaceful demonstration'.[193]

Animal advocacy organization Proefdiervrij continued to be active throughout this period but focused more and more on co-financing alternatives in research and pro-

188 Tweede Kamer Stukken (2007-2008) Kabinetsvisie "Alternatieven voor Dierproeven" (30 168, nr. 4), 04/06/2008, 6.

189 Ibidem.

190 Smid, Stagnerend Dierproevenbeleid.

191 Ministerie van Binnenlandse Zaken en Koninkrijksrelaties, 'AIVD-publicatie "Dierenrechtenactivisme in Nederland, grenzen tussen vreedzaam en vlammend protest" - Publicatie - AIVD' (Ministerie van Binnenlandse Zaken en Koninkrijksrelaties, 2004) <https://www.aivd.nl/documenten/publicaties/2004/07/12/dierenrechtenactivisme-in-nederland-grenzen-tussen-vreedzaam-en-vlammend-protest>. For example, an organization responsible for a series of fires turned out to consist of only two individuals. Please note that the report is about animal activism against all kinds of nonhuman animal use, not specifically nonhuman animal experimentation.

192 Ministerie van Binnenlandse Zaken en Koninkrijksrelaties, 'Links activisme en extremisme, divers en diffuus, wisselvallig en wispelturig - Publicatie - AIVD' (Ministerie van Binnenlandse Zaken en Koninkrijksrelaties, 2013) <https://www.aivd.nl/documenten/publicaties/2013/09/02/links-activisme-en-extremisme-divers-en-diffuus-wisselvallig-en-wispelturg>, 9-11.

193 Ministerie van Justitie en Veiligheid, 'Dreigingsbeeld Terrorisme Nederland 52 - Rapport - Rijksoverheid.nl' (Ministerie van Algemene Zaken, 2020) <https://www.rijksoverheid.nl/documenten/rapporten/2020/05/07/tk-bijlage-dtn-52>, 33.

moting these alternatives as "better science" than on demonstrations against nonhuman animal abuse. On January 9, 2012, the organization announced in a press release that they would no longer organize protests. According to Marja Zuidgeest, who was the chair of Proefdiervrij at the time, they were stuck in the dilemma of "human v. animal".[194] She stated that it is difficult to claim that we should not test on nonhuman animals when the results of those tests lead to saving human lives; 'that is a discussion we want to leave behind us'.[195] Instead of entering into ethical discussions about what should happen in cases where human and nonhuman animal interests are not aligned, Proefdiervrij decided to focus only on stimulating "win-win" situations. The emphasis of their work shifted even further towards cooperation with scientists and towards developing innovations that will lead to better research in which nonhuman animals no longer play a role. Zuidgeest: 'That is something no one can be against'.[196] As part of their change in course, they also changed their logo:

Figure 2.14 Proefdiervrij's old logo. Source: Proefdiervrij.

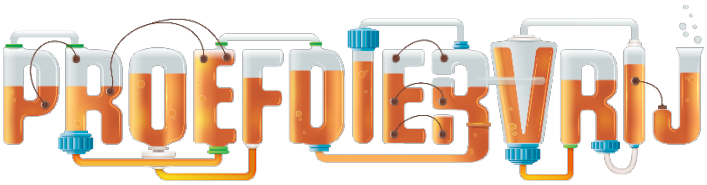

Figure 2.15 Proefdiervrij's new logo. Source: Proefdiervrij.

The change of strategy by some animal advocacy groups was also noticed by RIVM AEC secretary Arthur van Iersel:

> What you did see is that some of those groups maybe dealt smarter with the fact that, yes I am against [animal testing], but there is more than just being against it. Does that really achieve something, or can I contribute more by being for alternatives for the things that I am against. So you see that in the societal discussion, some of these groups have become smarter than just saying we are against it. By collaborating and making

194 Proefdiervrij: mens versus dier dilemma passé, Persbericht Proefdiervrij, 9 januari 2012.

195 Ibidem.

196 Ibidem.

> money available [...] An alternative for an animal test is of course only an alternative when it brings you better science. You are looking for a win-win situation.[197]

"Better science" is meant here to mean better scientific quality, referring to the fact that alternatives were only validated when their scientific quality was at least as good as the nonhuman animal test they were replacing. By emphasizing the better scientific quality of alternatives, activists (like the scientists cited earlier) hoped to motivate scientists more to move away from nonhuman animal testing than by focusing on nonhuman animal rights or welfare.

A trend analysis performed in 2009 showed that a majority of the population supported nonhuman animal testing for medical purposes.[198] People were found to be concerned about nonhuman animal welfare and primate welfare in particular, but society had also become increasingly risk-averse and human safety was in general perceived to be more important than nonhuman animal welfare[199]. Two topics that occasionally entered the public debate during this period were the use of primates and transparency. These are discussed below, followed by a brief discussion of the most recent developments.

The Use of Primates[200]

In 2000, the primate committee of the KNAW advised that the use of great apes be banned in research in the Netherlands. They argued that there were strong ethical reasons for doing so and that many other European countries had also already banned the use of great apes. If the option to contract out research with primates to facilities in the US (in case of a public health crisis) was kept open, they saw no need to keep a colony of great apes in the Netherlands.[201]

The proposal to amend the Animal Testing Act in this way was widely supported politically. The party *ChristenUnie* (Christian Union) stipulated that their vote in favor was not based on the idea that great apes are most closely related to humans in an evolutionary sense: 'This conviction (*geloofsbelijdenis*) is assumed by the government to show the suitability of great apes for medical research. Opponents of nonhuman animal testing with these species use the same argumentation to plead for abolishment of these tests.'[202] This citation nicely illustrates the paradox mentioned before wherein nonhuman animals have to be both similar enough to and different enough from humans to justify their use in experiments. For great apes, it was decided that the bal-

197 Interview Van Iersel.

198 J. T. de Cock Buning and others, 'Maatschappelijke trendanalyse dierproeven 2009 deel A en deel B.', 2009 <https://research.vu.nl/en/publications/maatschappelijke-trendanalyse-dierproeven-2009-deel-a-en-deel-b> [accessed 5 March 2021].

199 Ibidem; Schiffelers, Animal testing.

200 Only the national level is discussed here, since the use of primates at the RIVM is discussed in the next chapter.

201 'Primaten Voor Biomedisch Onderzoek — KNAW' <https://www.knaw.nl/nl/actueel/publicaties/primaten-voor-biomedisch-onderzoek>. Without the colony, research using great apes would have been impossible as importing great apes was not an option (see next chapter).

202 Tweede Kamer Stukken (2002-2003), 28503 'Wijziging van de Wet op de dierproeven, nr. 4, 06/11/2002, 4. Available online at https://zoek.officielebekendmakingen.nl/kst-28503-4.html.

ance fell in their favor and in 2002 the Dutch government announced a ban on using great apes in research starting immediately. The exception were five chimpanzees that were part of an experiment being performed in that moment at the Biomedical Primate Research Center (BPRC) in Rijswijk; the 105 other chimps living there had to be re-housed.[203] According to Minister Els Borst, medical experiments on great apes were no longer necessary in the Netherlands.[204] While animal advocates were of course in favor of the ban, there was also disappointment that not all primate research was banned. They were also disappointed that some chimpanzees stayed at BPRC and that forty-one were moved to zoos (with particular concern about the ones that were sent to a zoo in China).[205] Borst additionally stated the ambition to phase out all primate use but claimed that this was not possible in that moment because of a lack of alternatives. Instead, much to the dismay of animal advocates, the funding for BPRC was increased so that they could improve their housing.

The issue of nonhuman primates stayed on the political agenda and, in 2014, KNAW published the report 'The Use of Nonhuman Primates (NHP) as Test Animals: Benefits and Necessity?' The report concluded that research on primates was still both necessary and acceptable.[206] Parliament did not accept this report however because the KNAW also performed experiments on primates and was therefore not deemed independent.[207] The Rathenau Institute was asked by the ministry of OCW to also investigate the issue and, in 2017, they presented the report 'From Ape to Better' (*Van Aap naar Beter*). According to the report, it was requested by the Ministry of Education, Culture and Science (*OCW*) because Parliament had expressed the desire for experiments with nonhuman primates to be reduced to zero in the Netherlands—an important side note is that this should not have adverse consequences for public health. Based on stakeholder dialogue, the researchers concluded that using primates was no longer accepted by society and that all stakeholders agreed that phasing out primate use was a goal worth pursuing.[208]

With regard to how to achieve this, the report concluded that the 3Rs were not enough, especially not when seen as one-to-one replacements of primate tests. What was needed, (here it is again) was 'better science through lab animal free innovations'. In elaborating on this, they introduced the 3Bs instead of the 3Rs: Better science, better

203 VAN EEN ONZER VERSLAGGEVERS. "Einde aan proeven op mensapen". Algemeen Dagblad, July 3, 2001. advance-lexis-com.proxy.library.uu.nl/api/document?collection=news&id=urn:contentItem:48KK-PMR0-0150-X384-00000-00&context=1516831. Accessed March 5, 2021.

204 Slok/H Van Lierop/Halkema. "KABINET Verbod op dierproeven met mensapen". Algemeen Nederlands Persbureau ANP, March 15, 2002. advance-lexis-com.proxy.library.uu.nl/api/document?collection=news&id=urn:contentItem:45CK-9310-00B0-731G-00000-00&context=1516831. Accessed March 5, 2021.

205 "Verbod proeven mensapen; dierenbescherming baalt". Rotterdams Dagblad, March 16, 2002. advance-lexis-com.proxy.library.uu.nl/api/document?collection=news&id=urn:contentItem:48KK-SNS0-0151-12V1-00000-00&context=1516831. Accessed March 5, 2021.

206 KNAW, Gebruik van Niet-Humane Primaten (NHP) Als Proefdier — KNAW (Amsterdam, 2014) <https://www.knaw.nl/nl/actueel/publicaties/gebruik-van-niet-humane-primaten-nhp-als-proefdier>.

207 Ingrid Geesink, Lisa van Bodegom en Melanie Peters, Van aap naar beter - Een verkenning en dialoog over proeven met apen. Den Haag, Rathenau Instituut 2017

208 Ibidem. The report refers to the Eurobarometer 2010 in which respondents were asked if they supported using primates in research if it resulted in health benefits for humans. 45% agreed, 39% disagreed.

regulations, better answers to social questions.[209] So far, the 3Bs do not seem to have caught on however.

Transparency

According to Holmberg, questions of secrecy and openness often arise for those working in nonhuman animal experimentation. Openness can on the one hand lead to more public understanding but on the other hand may expose institutes and people to animal activism and reputation damage. 'Transparency' came out of the 2005 evaluation of the Animal Testing Act as one of the issues where a lot of improvement was needed.[210] This conclusion was supported by animal activists, who had already tried to affect more openness about nonhuman animal experimentation through lawsuits (see Chapter 4), but certainly not by all scientists. Van Iersel, who was part of the evaluation, recalls: 'It said that more publicness would be good, but many scientists turned against this. But then I think, if your research cannot pass public scrutiny, then think for yourself what you are not doing right'.[211] While he understood the concern about openness making one a target for activists, he expressed that more transparency can also create a playing field where activism has much less of a chance, because you can justify what you are doing.

In 2004, the Foundation Information Animal Testing (*SID*) was created with the aim of meeting the need for more information about nonhuman animal testing in the Netherlands.[212] In 2008, the KNAW, VSNU (Association of Universities in the Netherlands) and NFU (Federation of Dutch University Medical Centers) wrote and signed the Code for Openness in Animal Testing, expressing a commitment to more transparency, for which they saw a great need in society.[213] From the written explanation to the code, however, we can gather that both the code and SID were about more than meeting a public need. They were also very much about levelling the playing field mentioned by Van Iersel. In the explanation to the code, we can read:

> Until 2005, organizations that fundamentally resist animal testing, largely had a monopoly position on the 'information market'. Information about the why of animal testing and the societal benefits that they yield, was hardly available to the public. There was also hardly any information about the how of animal experiments and about the ethical weighing that is performed.[214]

By having more control over the information that reaches the public, the authors hoped to create more support and understanding for the nonhuman animal experiments that they still saw as necessary. By 2014, more openness became legally required when the EU directive of 2010 came into effect (Chapter 4).

Within the RIVM, openness about nonhuman animal testing was also a theme that featured regularly. In an email about a joint event with Proefdiervrij in 2002, Hendriksen explained that their open-door policy was one reason for their good relations with

209 Geesink et al., Aap naar Beter, 21.

210 This is discussed extensively in chapter 4.

211 Interview Van Iersel.

212 Stichting Informatie Dierproeven <https://www.stichtinginformatiedierproeven.nl/>.

213 The code can be found here: 'Code Openheid Dierproeven' <https://www.vsnu.nl/code-dierproeven.html>.

214 Code Openheid Dierproeven – KNAW, VSNU, NFU, 2008, 5.

animal protectors and good PR (see next chapter for an example). In addition, he stated that as a government agency they had an extra responsibility to be open about their policy.[215]

In 2006, RIVM animal technician John Boere wrote a letter about how the positive aspects of lab animal use should be presented better to the public to counterbalance the mostly negative press. In an email to the Advice Group on Lab Animal Policy, he explained that he was inspired to do so at the AALAS conference, where two members of the British organization PRO-test talked about their counter-offensive against the anti-lab animal organizations.[216] Even though Boere did not want to go as far as start such an organization in the Netherlands, he expressed wanting to see that AT's and animal caretakers also contributed to the awareness among the Dutch people that lab animals were well taken care of.[217] The following is a short fragment of his letter 'Where is the limit'.[218]

> What can we (the Article 9, 12 and 14 officers) do to get the limits clear for the Dutch people? Offering openness about the use of lab animals and verbal resistance to opponents of the use of lab animals. For years we have kept our mouths shut because that had been whispered in our ears. If we speak about our work at family meetings or in the sports club café and so forth, then say that we take better care of our lab animals than is the case for many pets. Also say that there are many diseases still that cannot be cured, and that very many diseases that can be cured, that this has been achieved through a contribution of research on animals. With this we can contribute ourselves to the public acceptance of research on animals and the limits thereof. Because we can all say that we want to replace animal testing by alternative methods, but for the foreseeable future we cannot do without animal research. That is a societal fact.

At that moment the RIVM was moving away from nonhuman animal testing, a policy not in line with the message expressed by John Boere. The Advisory Group on Lab Animal Policy discussed the letter in their meeting and agreed that it should not be published in connection with the RIVM but published solely on behalf of John Boere.[219]

Recent Developments

While a small group of activists has stayed concerned with nonhuman animal testing, society in general seems to have lost interest recently. In 2020, when transition experts of DRIFT researched the "landscape" in which the transition to animal-free innovation is supposed to take place, they were rather surprised. Researcher Jan Rotmans:

> Never before have I seen the government instigating a transition. The

215 Email from Coenraad Hendriksen to A. Lijdsman, 27/02/2002, RIVM Archive, file no. 2000349279.

216 Email from John Boere to A Henke: tekst voor biotechniek, 20/11/2006, RIVM Archive, file no. 1213.

217 Ibidem.

218 Attachment to the email from John Boere to A Henke: tekst voor biotechniek, 20/11/2006, RIVM Archive, file no. 1213.

219 Verslag vergadering Adviesgroep Proefdierbeleid, 13/12/06, RIVM Archive, file no. 1213.

> subject of animal-free innovation is not an issue within society but apparently is for politicians and policy makers. I never hear anyone about this subject during birthday parties![220]

Their transition analysis showed that a change in thinking about nonhuman animals within society played a role in a very general way, as a background to the transition, but not specifically in relation to nonhuman animal testing.

Summary

During this period, we saw a stagnation of the reduction in nonhuman animal testing that had started during the previous period and an increase of nonhuman animals killed in stock due to the popularization of transgenic animals. The RIVM deviated from this national trend as their tasks changed, and they ended up no longer being a license holder under the Animal Testing Act in 2009. Within Laboratory Animal Science and alternatives policies, the 3Rs have remained the dominant discourse and were presented as the solution to the problem of animal testing, by creating "win-win" situations: better science and better for the animals. The changing tasks meant that RIVM had to find a different focus in the (inter)national field of Laboratory Animal Science to maintain their position as experts. They shifted their focus from expertise in caring for lab animals and developing alternatives to validation and implementation and advising on policy and regulations. Society at large remained supportive of nonhuman animal experimentation for medical purposes, except for the use of great apes. This was banned in 2002 and the use of other primates continued to be a contentious topic. The resurgence of animal activism that we saw in the late 1980s continued during the beginning of this period, with a small minority of activists resorting to illegal action. From 2009 onwards, however, this latter type of protest largely disappeared and animal advocacy groups have taken the course of protesting through official channels and adopting a 'better science' discourse. Very recent research has shown that for the public in general, nonhuman animal experimentation is not a big issue at the moment. The TPI program, where the focus is on better, human-based science that is "by the way" without nonhuman animals, is mostly driven by politicians. As this program is only in its beginning stages, it is too early to say anything about what this will mean for nonhuman animal testing practices.

2.6 CONCLUSION

After this broad sketch of developments in nonhuman animal testing practices since 1950, it is now time to return to the questions posed in the introduction. Can any general conclusion be drawn about how practices of nonhuman animal experimentation and

220 Cited in: 'Hoogleraar Rotmans: Nooit eerder zag ik de overheid een transitie aanjagen - Nieuwsbericht - Transitie Proefdiervrije Innovatie' (Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2020) <https://www.transitieproefdiervrijeinnovatie.nl/actueel/nieuws/20/07/02/hoogleraar-rotmans-nooit-eerder-zag-ik-de-overheid-een-transitie-aanjagen>.

alternatives have developed during this period? We could argue that a great deal has changed regarding nonhuman animal testing practices and what we find acceptable: legislation has been created and revised limiting what is permissible; Laboratory Animal Science and the 3Rs (Replacement, Reduction, Refinement) have changed the way tested animals are obtained, housed, treated, and killed; "ethics" has become part of the discourse and an ethical review is now mandatory; and the intrinsic value of nonhuman animals is recognized. We could also argue that much has stayed the same: it has always been considered wrong to harm a nonhuman animal unnecessarily; while there is legislation, nonhuman animals remain objects in a legal sense; the view that experimenting on nonhuman animals is acceptable if it is in the interest of humans remains dominant and humans have continued to decide the permissibility of nonhuman animal experimentation; and large numbers of nonhuman animals continue to be subjected to animal experimentation. Both what has and what has not changed over time need to be pointed out to understand the experiences of humans and nonhumans in experimental practices during the different periods discussed. We can then see how discourses on acceptable nonhuman animal testing practices and regulations have been contested and adapted and we can also see continuity in other aspects (such as a clear distinction between humans and other animals), at least in the dominant discourse.

One important development is that nonhuman animal experimentation regulations are now widely accepted. Although the existence of nonhuman animal testing regulation is now unquestioned, we have seen that proposals for nonhuman animal testing legislation were met with resistance from scientists every time. By arguing that regulations would stand in the way of scientific progress and induce scientists to move their research abroad, they managed to keep legislation at bay for almost a century, until it was finally decided that the Animal Testing Act be created and accepted in 1977 (not least of all because of international peer pressure). Several amendments and revisions have followed since then. These were also initially met with resistance, but after acceptance and implementation of new legislation, resistance subsided and after a while these regulations became generally accepted as well. What was originally seen as a trade-off between human and nonhuman animal interests was reconstructed afterwards as a win-win for both. The win-win language was also clearly visible within Laboratory Animal Science and the 3Rs discourse, which was presented as the solution to the desire for scientific progress as well as a reduction of nonhuman animal testing. More recently, several stakeholders such as those united in TPI have begun to push a slightly different discourse, in which the focus is on "better science" based on human biology that is "by the way" without nonhuman animals. At the moment, however, the 3Rs remain the dominant discourse both in the Netherlands and internationally.

The 3Rs policies were created with the intention of reducing and refining nonhuman animal testing but, as we have seen, many other factors affected nonhuman animal use, with both intended and unintended consequences for the numbers of nonhuman animals used in research and the living conditions of those nonhuman animals. We saw that increased concern for public health and environment (heightened further by events such as the publication of Rachel Carson's Silent Spring and the Thalidomide tragedy) prompted increased safety testing. Transgenic animals were initially thought likely to enable a decrease of nonhuman animal testing, ("better models, less testing"), but actually caused a peak in nonhuman animal use and led to many more nonhuman animals being killed in stock. Conversely, reduction did not always come from alternatives. The strong-

est reduction in nonhuman animal testing came right after the first law, when alternatives research was just getting started, and thus was probably due to more careful consideration caused by mandatory registration and an economic recession. Specifically for the RIVM, we saw that many factors played a role in the steep reduction in nonhuman animal testing they experienced in the beginning of the 21st century.

How the permissibility of nonhuman animal experimentation developed was in part also related to changing human perspectives on nonhuman animals. We saw that in the 1950s nonhuman animals increasingly became objects of care and that in the 1980s "ethics" entered the discourse, although it remained unclear what exactly was meant by 'ethics' in this context (see also Chapter 5). This meant that nonhuman animal testing came to be seen as 'good science' only when lab animals were well cared for and when experiments were submitted to an ethical review determining their permissibility. What did *not* change over the years is the view that experimenting on nonhuman animals is acceptable and in part indispensable scientific practice, provided certain conditions are met, and that it is up to humans to determine the permissibility of nonhuman animal experiments. This is again related to views on nonhuman animals. While there certainly have been developments since the 1900s in how humans think about other animals, these developments have occurred within an anthropocentric perspective, rather than moving beyond it.

Coming back to the question of the nonhuman animals experimented upon, we can now ask: what have all these developments meant for nonhuman animals? But also: which continuities can be identified and what have those meant for nonhuman animals? Advances in Laboratory Animal Science, such as improved hygiene and refinement measures, have had a huge impact on the individual lives of many tested animals (e.g., through improvement of living conditions or the practicing of humane endpoints). In some cases, alternatives reducing or replacing nonhuman animal testing have resulted in certain animals not being brought into existence at all. However, sometimes an alternative test meant that the nonhuman animals which were bred and used otherwise would not have existed (e.g., when 'lower' animals replaced 'higher' animals. See Chapter 3 for an example of rats replacing monkeys). This last example shows the limits of thinking of all lab animals as one group, or even as one number, instead of individuals.

CHAPTER THREE

The Polio-monkeys

CHAPTER 3: THE POLIO-MONKEYS

3.1 INTRODUCTION

'Primate testing in the Netherlands down by nearly 50%![1]' read the recent headline of a short article published by Plant Based News. Indeed, in 2016, only 120 nonhuman primates were used in the Netherlands for biomedical testing, compared to 234 in 2015.[2] In addition, the Dutch government holds the political ambition to eliminate nonhuman primate use as soon as possible.[3] A government commissioned research report entitled 'From Ape to Better' (*Van Aap naar Beter),* produced by the Rathenau Institute, concluded that there is consensus among researchers on the use of nonhuman primates no longer being desirable and, indeed, being unacceptable to society. In other words, the use of nonhuman primates is now controversial in the Netherlands. This was not always the case, however. Views on nonhuman primates and their use for medical experimentation have changed over the past century.[4] Primate research, along nonhuman animal research in general, became booming business in the 1950s. Primate centers with colonies and breeding programs were established to ensure a continued supply of nonhuman primates for medical research.[5] The polio vaccine was a major reason for the increased use of primates; millions of monkeys were used worldwide, first for the development and later for the production and testing of polio vaccines. In 1963 in the Netherlands, 1550 out of 1800 monkeys used in experiments were used to produce the polio vaccine.[6] Three years later, the number of monkeys used for testing the polio vaccine had increased to 5887.[7]

In this chapter, I look at the use of nonhuman primates at the RIVM. Specifically, I analyze the use of long-tailed macaques for the production and control of the polio vaccine— as most RIVM monkeys were used for this purpose.[8] These long-tailed macaques first arrived at the RIVM in 1958 from South-East Asia where they lived in the wild. RIVM scientists used the kidneys of these monkeys as a substrate for growing the polio virus, which was needed to make the vaccine. The monkeys were additionally used to

1 Emily Court, 'Primate Testing In The Netherlands Down By Nearly 50%', Plant Based News, 2018 <https://plantbasednews.org/culture/primate-testing-netherlands-down-50/>.

2 Ministerie van Algemene Zaken, 'Jaarverslag NVWA "Zo doende 2016" - Jaarverslag - Rijksoverheid.nl' (Ministerie van Algemene Zaken, 2018) <https://www.rijksoverheid.nl/documenten/jaarverslagen/2018/02/01/jaarverslag-nvwa-zo-doende-2016>.

3 Ingrid Geesink, Lisa van Bodegom en Melanie Peters, Van aap naar beter - Een verkenning en dialoog over proeven met apen. Den Haag, Rathenau Instituut 2017.

4 Ibidem; Anita Guerrini, Experimenting with Humans and Animals. (Baltimore: The Johns Hopkins University Press, 2003).

5 J. Erwin, Terry. Maple, and G. Mitchell, Captivity and Behavior: Primates in Breeding Colonies, Laboratories, and Zoos, Van Nostrand Reinhold Primate Behavior and Development Series (New York [etc.]; Van Nostrand Reinhold, 1979).

6 Tweede Kamer Stukken, verslag 19e vergadering 1964-1965 (15/12/1964), 768.

7 A.L. van Wezel et al., 'New Approach to the Production of Concentrated and Purified Inactivated Polio and Rabies Tissue Culture Vaccines.', Developments in Biological Standardization, 41 (1978), 159–68.

8 Other uses of RIVM monkeys included: transplant research, ATG safety testing, developing a recombinant DNA measles vaccine, and heroin inhalation test.

test the safety and potency of the vaccine. Although perhaps not seen as an ethical issue at the start, the use of such large numbers of monkeys was problematic from the outset. As more and more countries began importing macaques for medical research, the monkeys became increasingly difficult to obtain. Motivated by this 'monkey-problem', RIVM researchers developed ways to make large-scale vaccine production more efficient, resulting in a dramatic decrease in the number of monkeys they needed. It would not be until 2005, however, that the polio vaccine production and control process became completely monkey-free. In this chapter, I will show how and why the use of monkeys changed and what these changes meant for the daily lives of these Polio-monkeys.

Much has already been written about the polio vaccine. Stuart Blume has written several historical articles about the polio vaccine in the Netherlands, which I will draw on in this chapter. What makes this chapter different from existing work is its focus on a specific group of individuals that played an important part in the Dutch history of the polio vaccine: the RIVM 'Polio-monkeys' themselves. As described extensively in the first chapter of this thesis, nonhuman animals often only feature in the margins of historical research, leading to anthropocentric histories.[9] In an attempt to avoid such anthropocentrism, I will place attention on both human and nonhuman primates as embodied individuals living entangled lives across species, something that is missing from the many existing histories of polio. Telling the stories of the Polio-monkeys means paying attention to their day-to-day lives, their interactions with each other and with humans, and their deaths. Understanding how their stories developed over time requires an analysis of the changing context of developments within the RIVM and, at the macro-level, broader developments and structures within science and society.

Zooming in on this specific case will allow me to flesh out the many different factors influencing the use of monkeys for polio vaccine production at the RIVM and how these factors interplayed. This will show that, initially, monkey shortages and economic concerns were the main motivations for shifting away from the use of monkeys. After 1980, the new Animal Testing Act (*Wet op de Dierproeven*) together with 3Rs discourse, and changing ethical perspectives on primate use led to increased attention to the welfare of RIVM monkeys. From this period onward, we see attitudes towards nonhuman primates changing as, in Dunayer's terms, law and society became more new- and less old-speciesist.[10] The use of nonhuman primates became more and more controversial and replacing them with 'lower animals' became an important focus within nonhuman animal experimentation. The monkey-breeding program that had started in 1979 also brought more attention to monkey welfare as a smaller number of humans and macaques now interacted much more intimately and for a much longer time. Despite these developments, it would not be until 2005 that the use of monkeys for the polio vaccine experimentation ended, although this was technically possible as early as 1982 when the Merieux Institute in France made the switch from monkey kidney cells to a continuous cell line. As we will see, risk aversion was an important barrier to change when it came to making this switch in the Netherlands.

In this chapter, I first set the scene for how polio vaccination started in the Nether-

9 Abigail 1972- Woods and others, Animals and the Shaping of Modern Medicine: One Health and Its Histories, Medicine and Biomedical Sciences in Modern History, 1 online resource (xvii, 280 pages): illustrations vols (Cham: Palgrave Macmillan, 2018) <http://doi.org/10.1007/978-3-319-64337-3>.See Chapter 1.

10 Joan Dunayer, Speciesism (Derwood, Md: Ryce Pub, 2004).

lands and consider what made this possible, including a brief historical background of polio vaccine research (Section 2). Next, I discuss how the first monkeys arrived at the RIVM and the adaptations necessary for accommodating for them (3). Section 4 analyzes how and why the vaccine production process was adapted to reduce the number of monkeys necessary, including the creation of a 'monkey-breeding program' (5). Section 6 examines the Animal Testing Act and 3Rs policy, as well as protests against primate testing meant for polio vaccine production practices. The last section (7) considers how monkey use finally came to an end in 2005, followed by some conclusions which can be drawn from this history (8).

3.2 THE FIRST VACCINE

The disease poliomyelitis was first described in the 19th century and more and more seasonal outbreaks of poliomyelitis were reported in industrialized countries in the first half of the 20th century.[11] During this period, there was an increase in the average age of polio patients and, alongside, the severity of the symptoms. Only five to ten percent of people affected by polio experience symptoms. These symptoms are usually flu-like, but in 0.5–1% of cases the virus spreads to the nervous system, causing paralysis of the arms and legs and, in the worst cases, affecting the nerves of the respiratory system and resulting in death. People used to get infected with polio at a very young age, with usually mild or no symptoms, gaining natural immunity for the rest of their lives. Due to improved hygiene since the late 19th century, however, people became infected at a later age, with more severe symptoms. Since then, there have been regular outbreaks of epidemic, usually in the summer months ('polio season'). In the Netherlands, there were major epidemics in 1929, 1938, 1941, 1943, 1944, and 1952. The largest outbreak occurred in 1956, with a reported 2,206 cases.[12]

The disease instilled great fear in the public, affecting mostly children but also adults, including the popular US president, Roosevelt.[13] A media hype in the US ensued and this, in combination with the unpredictability of the disease and lack of understanding of how it spread, caused scientists to experience extremely high pressure to create a vaccine.[14] The 'battle against polio' was fought most strongly in the United States, where Albert Sabin at the Children's Hospital Research Foundation in Cincinnati and Jonas Salk at the University of Pittsburgh were in fierce competition to create the first vaccine

11 Guerrini, Experimenting with; Paul M. (Paul Maria) Oostvogel 1953-, 'Control of Poliomyelitis in the Netherlands: Towards Eradication of a Disease' (s.n., 1999). The disease poliomyelitis is caused by the poliovirus, a picornavirus, of which there are three different serotypes. It belongs to the subgroup of enteroviruses and targets the epithelial cells of the enteric tract. Humans are the only natural hosts, but other primates can also be infected. Non-primates lack polio receptors and are therefore not susceptible to the virus (with the exception of TgPVR mice, transgenic mice expressing the receptor for poliovirus).

12 Oostvogel, Control of Poliomyelitis.

13 At first polio was thought of as a 'white' disease, as (white) medical experts claimed that black people were not susceptible to the virus and that therefore treatment should only focus on white people. Although there was indeed a lower reported incidence of polio among black people, this was a consequence of medical racism (i.e. polio cases were missed because of limited access to health care) Naomi Rogers, 'Race and the Politics of Polio', American Journal of Public Health, 97.5 (2007), 784–95 <https://doi.org/10.2105/AJPH.2006.095406>.

14 David M. Oshinsky, Polio: An American Story (Oxford ; New York: Oxford University Press, 2005).

against polio.[15] Monkeys played a crucial role in this, as primates are the only nonhuman animals that can contract polio. Millions of monkeys were used and killed in the search for a vaccine.[16] Salk worked on a vaccine using inactivated or killed virus, usually referred to as IPV (Inactivated Polio Vaccine) or KPV (Killed Polio Vaccine). Sabin, however, was convinced that a live, attenuated (weakened) vaccine would be the only way to protect people from the virus. Indeed, many virologists at the time did not believe that a killed vaccine would be able to instill long term immunity.[17] Sabin developed a live vaccine called OPV (Oral Polio Vaccine), with the O standing for oral as it was given in liquid form on a sugar cube.

According to Sabin, none of his and others' work on elucidating the workings of the polio virus and creating a vaccine against it would have been possible without the work John Enders, Thomas Welles, and Frederick Robbins, for which they won the Nobel prize in 1954.[18] The group discovered that it was possible to grow poliomyelitis viruses in cell cultures of several types of tissue. Using these cell culture techniques, both Salk and Sabin were able to develop a potential vaccine, but Salk's vaccine was the first to be considered ready for testing on humans. Field trials with his IPV were held in 1954, followed by large-scale vaccination in 1955. Salk's field trials were financed by the National Foundation for Infantile Paralysis in the US ('March of Dimes') and when his trials proved successful, the Foundation advised Sabin to stop his efforts to develop his live vaccine.[19] However, many colleagues advised him to keep going, including the Dutch scientist Jacobus D. Verlinde who was head of bacteriology and experimental pathology at the Dutch Institute for Preventive Medicine (*NIPG*) in Leiden.[20] Verlinde conducted small studies in the Netherlands with Sabin's OPV, using families of lab physicians and other personnel as test subjects. The most extensive field trials with OPV, however, were however conducted in the USSR.[21]

The Dutch eagerly followed these overseas developments as polio epidemics continued. As the future head of the polio laboratory of the RIVM Bart Hofman put it in a 1956 lecture, '[…] almost not a day went by [in the US] or one could read about this disease in the newspapers. It was "headline stuff". And now we are experiencing the same in the Netherlands, albeit in a slightly less loud manner.'[22] There was, however, also apprehension about the risks of the vaccine. According to Hofman, the Netherlands had to carefully consider the possibility and desirability of vaccinating against polio.[23] In May of 1956, Director General of Public Health Prof. P. Muntendam expressed still feeling that there were too many uncertainties connected to the vaccine for the government to

15 Stuart Blume and Ingrid Geesink, 'A Brief History of Polio Vaccines', Science, 288.5471 (2000), 1593–94 <https://doi.org/10.1126/science.288.5471.1593>.

16 Guerrini, Experimenting with.

17 Blume & Geesink, A Brief History.

18 Albert B. Sabin, 'Oral Poliovirus Vaccine: History of Its Development and Use and Current Challenge to Eliminate Poliomyelitis from the World', The Journal of Infectious Diseases, 151.3 (1985), 420–36 <https://doi.org/10.1093/infdis/151.3.420>.

19 Sabin, Oral Poliovirus Vaccine.

20 'In Memoriam Prof.Dr.J.D.Verlinde. | Nederlands Tijdschrift Voor Geneeskunde' <https://www.ntvg.nl/artikelen/memoriam-profdrjdverlinde/volledig>.

21 Sabin, Oral Poliovirus Vaccine.

22 Lecture 'Immunisatie tegen polioyelitis' by Bart Hofman, 1956 RIVM Archive, file no. 1017459V

23 Ibidem.

begin vaccinating 'in the near future'.[24] This changed quickly with the outbreak of the largest ever epidemic of 1956 and the successes obtained with vaccines in the US. The first vaccine available in the Netherlands was the Belgian RIT-vaccine, approved by the RIVM.[25] This vaccine was available by doctor's prescription for individual patients and through local health services that did not want to wait until national vaccination started.[26] The National Health Council decided to start vaccinating nationally in 1957.[27] All 220,000 children born in 1955 were vaccinated that September. Later, children born in earlier years followed. After vaccination started, the incidence of polio dropped spectacularly.[28] Despite a high level of vaccination (around 95% of the population), small epidemics still occurred in the Netherlands after 1957, most recently in 1992. These epidemics always occurred in highly religious communities, where many people refusing vaccination lived close together (along the so-called 'bible belt'), making it impossible for herd immunity to be reached.[29]

The start of nationwide IPV vaccination also marked the start of the National Vaccination Program in 1957 (*Rijksvaccinatieprogramma*, *RVP*), which included not only the inactivated polio vaccine but also vaccines against diphtheria, tetanus, and pertussis (DTP), for all of which vaccination had started earlier. The RIVM was responsible for vaccine production and control. Since investments had already been made into large-scale production of the DTP vaccine, the shift to local production of IPV did not necessitate great changes in laboratory equipment.[30] It did however require that new facilities be built and new staff be hired to house and take care of large numbers of monkeys, since the DTP vaccine had been made using non-human animals other than monkeys.

For practical and economic reasons, the RIVM would have preferred to use a smaller and cheaper testing species than monkeys. However, this was impossible at the time given that non-primates are not susceptible to the poliovirus and scientists had not yet succeeded in creating other animals with poliovirus receptors (though they were trying with mice). The use of monkeys for the production of polio vaccines was not met with much public resistance at the time.[31] Nonhuman animal testing had become

24 "GEEN POLIO VACCIN IN NEDERLAND". "Het nieuws: algemeen dagblad". Paramaribo, 1956/05/30 00:00:00, p. 3. Geraadpleegd op Delpher op 24-02-2021, http://resolver.kb.nl/resolve?urn=ddd:010473205:mpeg21:p003.

25 The Belgian vaccine was chosen as standards were believed to be higher than in the US. Ulrike Lindner and Stuart S. Blume, 'Vaccine Innovation and Adoption: Polio Vaccines in the UK, the Netherlands and West Germany, 1955–1965', Medical History, 50.4 (2006), 425–46 <https://doi.org/10.1017/S0025727300010279>.

26 "Belgisch vaccin tegen polio al verkrijgbaar In september massa-proefinenting met Amerikaans vaccin". "De waarheid". Amsterdam, 1957/05/11 00:00:00, p. 3. Geraadpleegd op Delpher op 24-02-2021, http://resolver.kb.nl/resolve?urn=ddd:010370014:mpeg21:p003

27 Stuart S. Blume, 'Lock in, the State and Vaccine Development: Lessons from the History of the Polio Vaccines', Research Policy, 34.2 (2005), 159–73 <https://doi.org/10.1016/j.respol.2004.12.001>.

28 Oostvogel, Control of Poliomyelitis.

29 IPV does not induce contact immunity, but it does induce herd immunity, which protects unvaccinated individuals by reducing their chances of coming into contact with the virus. OPV does induce contact immunity, but given that most people refusing vaccination lived in close-knit communities, there was very little chance for contact-immunity to occur. OPV was used in addition to IPV in cases of epidemic to quickly vaccinate people in communities affected by an outbreak. Letter from Dr. J. Wester (Chair of the health council), to Dr. G.M.J. Veldkamp, Minister of Social Affairs and Public Health. The Hague, 28/06/1963. RIVM Archive, file no. 1020190.

30 Blume, Lock in.

31 Guerrini, Experimenting with.

standard scientific practice in the 1950s and anti-vivisectionism was at a low (see also the previous chapter). The use of monkeys (or any other animals) is not mentioned as ethically problematic in any of the RIVM archival materials from the 1950s and 1960s.

In short, the vaccine was highly desired, the facilities, technoscientific abilities, and (government) financing were available, and objections were (largely) absent. In the next section we will see how the first monkeys arrived in Bilthoven, the Netherlands.

3.3 THE FIRST MONKEYS

The polio vaccine was initially imported from outside countries, including Belgium and the US.[32] Simultaneously, preparations were begun for local production of the vaccine using long-tailed macaques. Their kidney cells were to be used as a substrate for the poliovirus to grow on before it was inactivated to make IPV. To make enough vaccine for the entire country, the RIVM needed as many monkey kidneys as virus substrates. Additional monkeys were used to test the safety and potency of the vaccine, though not numbers as high as those needed for the vaccine production.

While the RIVM had experience with vaccine production and nonhuman animal testing, the use of large numbers of monkeys was new and meant that substantial preparation time and effort were needed. Plans were made to convert old horse stables into monkey stables. Taking care of these monkeys would require extra staff and at first the main focus was on designing monkey stables in such a way that care-taking required as little labor as possible.[33] Therefore, in October 1958, it was proposed that six to eight monkeys by housed in cages which measured 1.0 by 1.2 meters and 2 meters high.[34] Eight such cages were to be placed in a single stable, making it possible to house about fifty-six monkeys in one stable. As building these new stables would require at least a year, temporary housing was created so that production of the vaccine could begin.[35] By January 1959, the RIVM Board of Directors had decided they preferred a system of two monkeys per cage over group housing for reasons of hygiene and control, even if this meant higher staff expenses.[36] The new plan was to have twenty-four cages (and forty-eight monkeys) in one stable. This way, a total of almost six hundred monkeys could be housed at the same time. In March, the number of cages per stable was increased to thirty, requiring twelve men to care for the monkeys and clean the cages.[37] However, placing thirty cages (in two layers of fifteen) in one stable made it impossible to also have a large enough entrance sluice. Therefore, they decided to have three layers of cages and thirteen cages per layer, making for a total of thirty-nine cages per stable. This can be

32 'Correspondentie & offertes', RIVM Archive, file no. 1020190.

33 Verslag vergadering 20/10/1958 'Inrichting Apestal', with Cohen, Kruijt, Koopmans. RIVM Archive, file no. 1017555.

34 Verslag vergadering 20/10/1958 'Inrichting Apestal', with Cohen, Kruijt, Koopmans. RIVM Archive, file no. 1017555.

35 Verslag vergadering December 1958 'Inrichting Apestal', with Cohen, Kruijt, Koopmans. RIVM Archive, file no. 1017555.

36 Verslag vergadering januari 1959 'Inrichting Apestal', with Cohen, Kruijt, Koopmans. RIVM Archive, file no. 1017555.

37 Verslag vergadering maart 1959 'Inrichting Apestal', with Cohen, Kruijt, Koopmans. RIVM Archive, file no. 1017555.

seen in the drawing plans below.[38] The temperature was to be kept constant at twenty-five degrees Celsius (or warmer in the summer). The lower right-hand corner of the plans shows the entrance sluice, where employees had to change to avoid contamination.

The RIVM used Cynomolgus monkeys for polio vaccine production, also known as long-tailed macaques or crab-eating macaques. These monkeys originated from regions throughout Southeast Asia but had also been introduced to other regions (such as Mauritius) by humans. They are social animals who live in groups along matrilineal lines.[39] They often lived in areas also populated by humans, and a variety of human-macaque relations have developed over time. In some areas, humans considered the monkeys to be sacred and treated them accordingly, while in other areas there was fierce competition over resources between the two species.[40] Unfortunately for the monkeys, they were also very popular among scientists who wanted to use nonhuman primates in research. The Cynomolgus' similarity to humans made them interesting as research animals and as discussed above, in the case of polio, they were the only other animals that could contract the disease. Not all nonhuman primates are as similar to humans as has sometimes been assumed, however. Indeed, faulty assumptions along these lines has resulted in misleading research results, including in polio research in the 1930s. A great deal of time was wasted in the US in the 1930s by using Rhesus monkeys to research the nature of the disease. These monkeys only contract polio when the virus is injected into the spinal cord, leading researchers to believe that infection happens via the spinal cord in humans as well when in fact humans are most often infected by ingesting the virus orally.[41]

For the production of polio vaccine, the RIVM used Cynomolgus monkeys imported by Dutch commercial supplier Van der Bijl from Indonesia and Malaysia.[42] In later years, the RIVM also used other species of monkeys for polio vaccine production and control, including rhesus monkeys, African green monkeys, and patas monkeys.[43]

38 Verslag vergadering 30/12/1959 'Inrichting Apestal', with Cohen, Kruijt, Koopmans. RIVM Archive, file no. 1017555.

39 Sandrine MJ Camus and others, 'Birth Origin Differentially Affects Depressive-Like Behaviours: Are Captive-Born Cynomolgus Monkeys More Vulnerable to Depression than Their Wild-Born Counterparts?', PLOS ONE, 8.7 (2013), e67711 <https://doi.org/10.1371/journal.pone.0067711>.

40 One recent study found groups of cynomolgus monkeys involved in something called 'robbing and bartering', where they rob tourists of something valuable (often glasses) and give it back in return for food. Fany Brotcorne and others, 'Intergroup Variation in Robbing and Bartering by Long-Tailed Macaques at Uluwatu Temple (Bali, Indonesia)', Primates, 2017, 1–12 <https://doi.org/10.1007/s10329-017-0611-1>.7.

41 Guerrini, Experimenting with.

42 It is possible that other suppliers were used as well, which were not mentioned in archives or articles. R. Boot, 'Pregnancy Diagnosis in Macaco Fascicularis', Journal of Medical Primatology, 10 (1981), 141–48; van Steenis G and others, 'Use of Captive-Bred Monkeys for Vaccine Production.', Developments in Biological Standardization, 45 (1980), 99–105.

43 In 1976, for example, five patas monkeys were purchased from the Merieux Institute to compare their cells to those of the Cynomolgus monkeys. They were not found to be more suitable, however. Letter from A.L. van Wezel to dr. Montagnon of the Merieux Institute on 4/6/1976. File number 1016589. A small breeding programme with African green monkeys was started; their kidneys were used for safety testing the vaccine. About six monkeys per year were born in this breeding program. Interview R2.

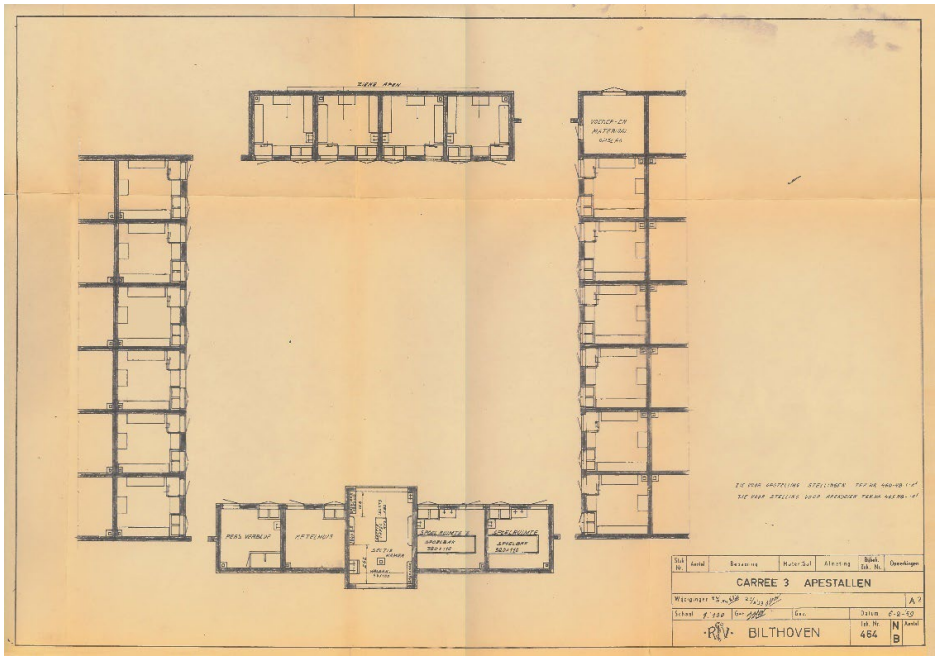

Figure 3.1 Layout of the monkey stables[44]

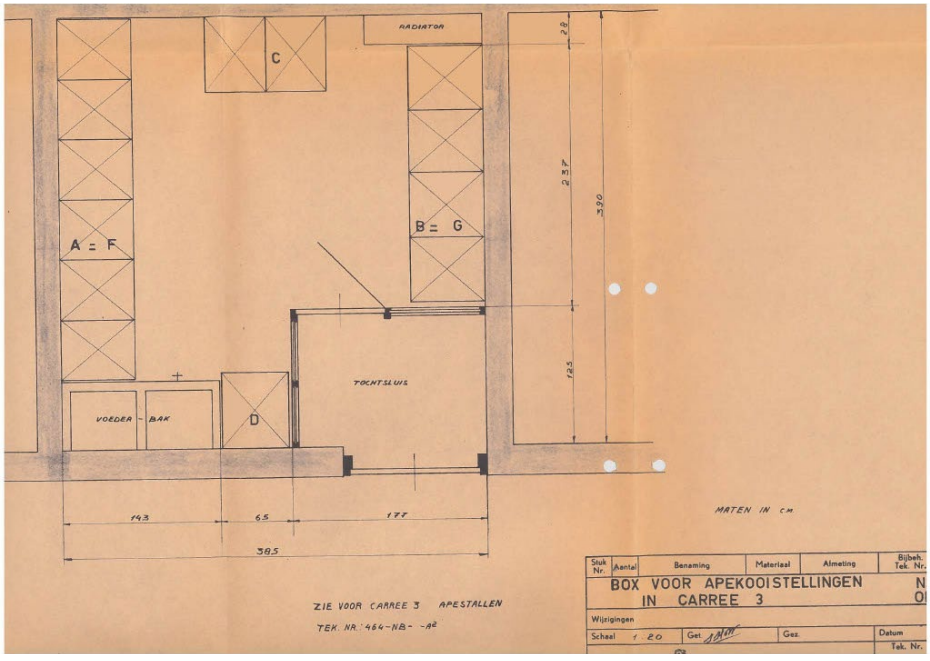

Figure 3.2 Layout of cages in the monkey stable[45]

The RIVM-macaques had number tattooed on their chests for identification purpos-

44 'Carree 3 Apestallen' 06/02/1959. RIVM Archive, file no. 1017555.

45 'Box voor apekooistellingen in carree 3' 24/12/1959. RIVM Archive, file no. 1017555.

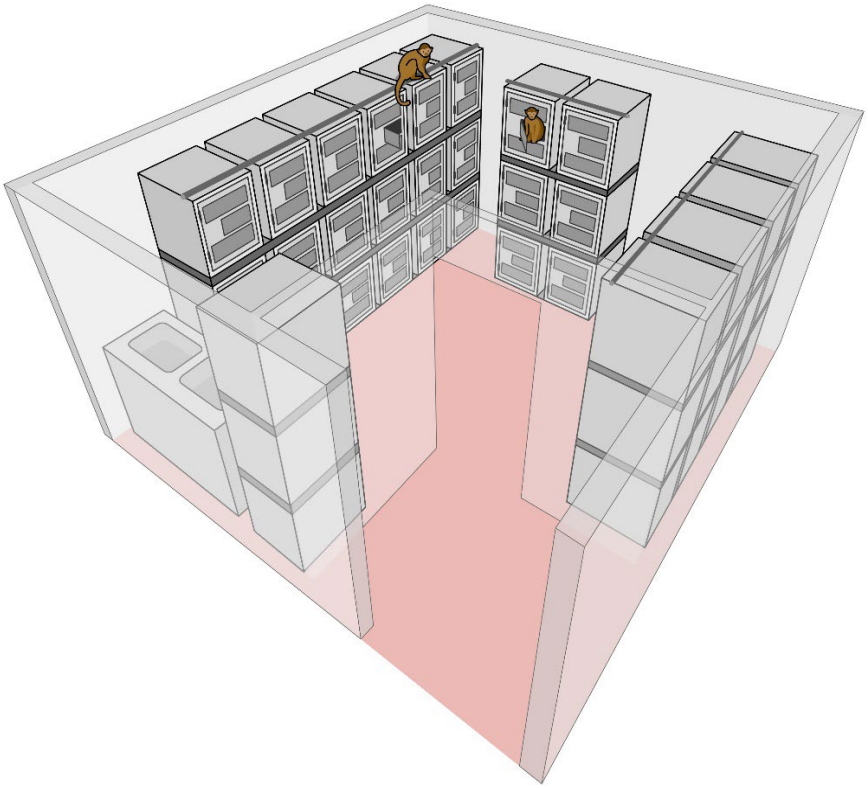

Figure 3.3 3D impression of a RIVM monkey stable based on the drawing in figure 19 and photographs of monkey cages. Created by Frank-Jan van Lunteren.

Figure 3.4 Monkeys in cages. Source: RIVM.

es.[46] Since the imported macaques had been caught in the wild, they had the potential to harbor all kinds of diseases. In addition, the stress that monkeys experienced as a result of being captured and transported could cause health problems and even death. For these reasons, the monkeys underwent extensive testing and (preventive) treatment upon arrival and shortly before the removal of their kidneys.[47] If monkeys were infected with anything, measures were taken to prevent infection from spreading to the staff and monkeys were quarantined to prevent spread to other monkeys. Despite these measures, disease and death among the monkeys remained a problem. Of the 109 monkeys received in August 1958, sixteen were found to be positive for tuberculosis. In another shipment of 350 monkeys delivered in 1958, over fifty died intercurrently.[48] Death rates were considered in the normal range at twenty percent and could sometimes be as high as fifty percent.[49] In addition, obtaining wild monkeys became more difficult. As a result, RIVM researchers were motivated to change the practice of IPV production so that they would no longer have to rely on large numbers of wild-caught monkeys.

3.4 THE UNIT PROCESS

While many countries opted for OPV when this became available, the Dutch continued to utilize IPV for their national vaccination program. They did not maintain the vaccine in exactly the form developed by Salk, however. RIVM polio vaccine development and production practices were constantly evaluated and reconfigured to improve vaccine effectiveness and make production more efficient. One of the first improvements was made in 1962, when the four vaccines (DTP and IPV) were combined into one quadruple shot.[50] Other improvements focused on developing a more efficient production process, requiring fewer monkeys, less space, and less labor, preventing infections, and making the vaccine more effective in bringing about immunization, so that less booster shots would be needed.

In the early 1960s, microbiological engineer Paul van Hemert developed the 'Bilthoven-Unit', named after the city where the RIVM is located. The Bilhoven-Unit contained four fermenters designed for submerged cultivation of microorganisms for vaccine production.[51]

This innovation marked the start of efficient and large-scale vaccine production. Since then, RIVM researchers have worked on improving the production process of IPV by turning it into what they called a "Unit Process". Another important scientific breakthrough was made by RIVM microbiological engineer Anton 'Toon' van Wezel, who

46 Verslag vergadering november 1958 'Inrichting Apestal', with Cohen, Kruijt, Koopmans. RIVM Archive, file no. 1017555.

47 'Proefdiervoorziening 1970-1980'. RIVM Archive, file no.1050042.

48 Verslag vergadering januari 1959 'Inrichting Apestal', with Cohen, Kruijt, Koopmans. RIVM Archive, file no. 1017555.

49 Project 13a: proefdiervoorziening, verslag periode 1-03-1974 tot 1-10-1974 by B.C. Kruijt, 18/10/1974 RIVM Archive, file no.1050042.

50 Oostvogel, Control of Poliomyelitis.

51 Paul van Hemert, 'The "Bilthoven Unit" for Submerged Cultivation of Microorganisms', Biotechnology and Bioengineering, 6.4 (1964), 381–401 <https://doi.org/10.1002/bit.260060403>.

Figure 3.5 The Bilthoven-Unit. Source: RIVM.

developed the microcarrier culture technique published in *Nature* in 1967.[52] Microcarriers are tiny beads (DEAE-Sephadex particles) that serve as a surface onto which primary cells—kidney cells of macaques in this case— can attach, making it possible to culture tissue cells in suspension rather than monolayer. This suspension can then be used as a substrate for virus multiplication. The new method replaced monolayer cell cultivation in Povitsky bottles, increasing the amount of virus that could be grown in one fermenter.

Trypsinization of monkeys' kidneys also made the production process more efficient. Trypsinization by the perfusion method was first developed by Kammer (published in 1969) and developed further for use in IPV production at the RIVM.[53] Perfusing the kidneys of the monkeys with a trypsin solution increased the cell yield obtained per monkey from 127 x 10^6 to 830 x 10^6 (see Section 3.5 for a schematic diagram of

52 A. L. Van Wezel, 'Growth of Cell-Strains and Primary Cells on Micro-Carriers in Homogeneous Culture', Nature, 216.5110 (1967), 64–65 <https://doi.org/10.1038/216064a0>.

53 Van Wezel et al. New Approach; Herbert Kammer, 'Cell Dispersal Methods for Increasing Yield from Animal Tissues', Applied Microbiology, 17.4 (1969), 524–27.

the perfusion process). These new methods, joined together in the Unit Process, led to a 'substantial decrease in manpower and animals needed for the production of polio vaccine at our laboratory'—from 5887 macaques in 1966 to 531 in 1976.[54]

The decrease in monkey use in the production of the polio vaccine also affected potency testing methods. In 1975, G. van Steenis wrote a letter to Director General H. Cohen saying that a point had been reached when more monkeys were used in potency testing than were needed for their kidney cells for virus cultivation. This meant housing these 'leftover' monkeys and taking care of them for a longer period of time without having any direct use for them. The process required 'manpower' and space, making it costly.[55] Therefore, Van Steenis argued that rats should replace monkeys in potency testing. However, in 1975, H.P. Lansberg pleaded with the European Pharmacopoeia on behalf of the RIVM to include a monkey potency test for the polio vaccine. Several arguments were given as to why monkeys were preferred as testing animals: the many years of experience with monkeys, the monkey test being demanded by the US, monkeys being closer to humans than any other species.[56] Here we see some tension between the desire to reduce costs and the desire to stay with a method that works. Yet despite arguments to the contrary, over time rats did replace monkeys in the potency tests, as experiments showed that using rats produced the same quality of results as using monkeys.

Despite the drastic reduction in monkey testing by the late 1970s, the RIVM was motivated to reduce monkey use even further. This would have obvious economic advantages given that wild monkey shortages were still an issue. By this point, however, it was not (just) a matter of a monkey shortages in the wild, but also a shortage of monkey availability for research due to import and export bans, as more attention was paid to natural conservation. Indonesia implemented stricter export rules and the Dutch government was soon expected (by the RIVM) to recommend a stricter policy regarding the import of primates.[57] This rising concern for 'natural conservation' in relation to primates can also be seen in the 1981 WHO International Primate Resource Program which states as its objective:

> [...] to develop international cooperation to support primate conservation and production in order to ensure the permanent existence of wild primate populations in their natural habitats, as well as to ensure the continuing provision of primates to meet human health-related needs.[58]

In the report, WHO proposes to manage wild populations of primates as 'renewable natural resources' and claims that 'countries possessing natural wild primate populations stand to benefit by the provision of carefully determined numbers of the animals for biomedical use, whether they be derived from controlled capture in the wild or from

54 Van Wezel et al. New Approach, 162.

55 Letter from Dr. G. van Steenis to Dr. H. Cohen 'Betreft: antigeniteitsproeven poliomyelitisvaccin' d.d. 26/06/1975. RIVM Archive, file no. 1017133.

56 Letter from Drs. H.P. Lansberg to Dr. G. van Steenis 'Betreft: antigeniteitsproeven poliomyelitisvaccin' d.d. 30/06/1975. RIVM Archive, file no. 1017133.

57 Project 13b: Ontwikkeling Apenkweek door R. Boot, oktober 1979-maart 1980 and march-october 1979, and nov. 1978-march 79. 78-80 RIVM Archive, file no. 1050042.

58 The WHO international primate resources program WHO/BLG/81.1 Rev.1 Annex 1. RIVM Archive, file no.1017219.

local breeding stations.'[59]

Despite WHO efforts to ensure a continued supply of primates for biomedical use by treating them as 'renewable natural resources', the RIVM preferred to be completely independent from foreign sources. They proposed to achieve this by using secondary monkey kidney cell cultures to further reduce the number of monkeys needed in testing and by starting a breeding program to produce home-bred monkeys—which could only be a feasible alternative if less monkeys were needed. Home-bred monkeys had the additional advantage of being 'cleaner' than wild monkeys.[60] In 1980, van Wezel et al. published an article entitled 'The production of Inactivated Poliovaccine on serially cultivated kidney cells from captive-bred monkeys', in which they described how they were using cultivated cells up to the 12th generation to reduce the need for monkeys from about fifty times to about five times per year.[61] Using continuous cell lines as a substrate was suggested as the most practical and economical choice, but this was something that was expected to take several years to become generally accepted and therefore did not provide a solution for 'the acute monkey problem of the present time'.[62] Thus, not only was the switch to producing the vaccine on cultivated kidney cells made, but additionally, from 1980 onwards, tertiary monkey kidney cells were used for some control measures (i.e. determining inactivation curves). For tissue safety tests, primary monkey kidney cells were still be used, requiring the perfusion of one monkey per fortnight.[63]

In improving the vaccine, the RIVM collaborated extensively with the Merieux Institute in France and with Jonas Salk at the Salk Institute in the US. Together they conducted field trials with improved versions of the IPV-vaccine, exchanged samples and technologies, conducted tests for one another, and organized conferences and lab visits. In 1977, they officially joined forces in the Forum for the Advancement of Immunization Research (FAIR). When FAIR was founded, the first objective was stated to be: 'Improved efficiency and economy in polio virus antigen production for inactivated vaccines'. Although FAIR was founded to focus on many aspects of immunization, its main goal was the promotion of the use of IPV, especially in developing countries, to support efforts to eradicate polio worldwide. A meeting was held in 1977 in Bilthoven on 'Immunisation against PolioMyelitis with inactivated PolioVirus Vaccine', during which Jonas Salk gave a lecture on 'The failures of OPV and successes of IPV'.[64] Salk obviously still had great faith in his vaccine and its potential to eradicate polio worldwide. Given that the Netherlands was one of the few countries where IPV was still being used (and successfully so) and that they had even managed to make the vaccine more effective and cost efficient, Salk looked to them for support in achieving his polio vaccine goals.

59 Ibidem.

60 Van Wezel et al., New Approach.

61 A. L. Van Wezel, C. A. Van Der Velden-De Groot, and J. A. Van Herwaarden, 'The Production of Inactivated Poliovaccine on Serially Cultivated Kidney Cells from Captive-Bred Monkeys.', Developments in Biological Standardization, 46 (1980), 151–58.

62 Van Wezel et al., The Production, 1.

63 Bespreking vervanging primaire apeniercellen voor controle doeleinden en diagnostiek, d.d.23/09/1980. RIVM Archive, file no.1016956. Perfusion in this case means flushing the kidneys with a trypsin solution, see 3.5 for a diagram.

64 Report of the Meeting on Immunization against Poliomyelitis with Inactivated Poliovirus Vaccine held on 28/12/1977 at the RIVM. 9/5/1978. Nationaal Archief, file no. 4287.

The Dutch government also seemed to remain convinced of the importance of IPV. In 1980, the Dutch government donated one million guilders to the WHO to be used for further studies of IPV. 400,000 guilders were informally earmarked for purchasing IPV from the RIVM (to be used in these studies).[65] Studies by WHO and FAIR were often conducted in countries with a tropical climate, as it had become clear that OPV did not always work well in tropical conditions.[66] At the International Symposium on Poliomyelitis Control in 1983, a discussion was held on OPV's failure to confer immunity to all vaccinated individuals in warmer countries such as India and occupied Gaza.[67] A possible 'comeback' of IPV was likewise discussed, as IPV's efficacy did not seem to vary by climate. IPV was still more expensive than OPV, however, partly due to the use of monkeys in the production process. Although the Dutch had managed to greatly reduce the number of monkeys needed for testing, for global production the method would still have required large numbers of monkeys. There was hope, however, that a continuous cell line could be the solution for this, which will be considered shortly. First, we will look at the RIVM breeding program and how changes in the production process affected the lives of the monkeys being used.

3.5 HOME-BRED MONKEYS

In the previous section, we have seen how RIVM researchers made groundbreaking developments in polio vaccine development and production practices. The breakthroughs reduced the number of monkeys used to such an extent that it became possible to start a breeding program which replaced the import of wild monkeys. This development had a great impact on the lives of the Polio-monkeys (and of course on the wild monkeys that might otherwise have been imported). While RIVM researchers certainly affected the RIVM monkeys' experiences, it was the animal technicians (ATs) and caretakers who were in day-to-day contact with them. As the discussion that follows will demonstrate, the breeding program's conception altered human-monkey interaction greatly.

Birke et al. argue that interactions between lab animals and human lab workers can reproduce as well as challenge a human/animal dichotomy.[68] When looking at the human-macaque interactions at the RIVM after the start of the breeding program, we see that they included individuals meeting and touching, multiple bodies becoming attuned and finding joined rhythms, but also forced movement, conflict, and killing.[69] Although the practice of nonhuman animal testing as a whole reproduces a human/animal dichotomy, at the micro-level of the RIVM laboratory challenges to this dichotomy also occurred.

In 1974, the RIVM started a breeding program with a small breeding colony in which

65 Note for the Record of 'Visit of Dr. Hans Cohen, Rijks Institute, Bilthoven, The Netherlands, 18/4/1980 by Dr. Ralph H. Henderson, Director EPI of WHO. Nationaal Archief, file no. 5772

66 'Correspondentie Salk na mei 1980'. RIVM Archive, file no. 1017053.

67 Ibidem; A. Rosenfeld, 'The Body: Polio Revisited', OMNI, 6.1 (1983), 44.

68 Birke et al. elaborate on Barad's concept of posthumanist performativity to show how it can be used to analyze the intra-actions of different human-animal dyads. They call these intra-actions choreography and use the dyad of the 'lab rat' and the 'scientist' as an example to show how intra-dyadic material-discursive practices can both reproduce as well as challenge a human/animal dichotomy. Lynda Birke, Mette Bryld, and Nina Lykke, 'Animal Performances', Feminist Theory, 5.2 (2004), 167–83 <https://doi.org/10.1177/1464700104045406>.

69 See Chapter 1 for an explanation of 'attunement'.

monkeys lived alone in a cage. Five years later, they expanded the program and switched to harem groups (ten groups of one male and ten to twelve females). The RIVM breeding program fit well within a larger international trend of research facilities starting their own breeding programs. When primate research first began, monkeys had been observed in the wild for "naturalistic observation". They were subsequently brought into local laboratories where colonies were established.[70] In the first half of the 20th century, these were referred to as 'colonies in colonies'.[71] In 1924, for example, Pasteur established a colony of chimpanzees in Kindia, French Guinea for both local use and for shipment to his research facility in Paris.[72] The 1950s and 1960s saw rapid growth and institutionalization of primate research, with seven large primate centers being established in the US which included breeding programs.[73] Many laboratories instituted breeding programs as a response to increasing awareness of conservation issues as well as to restrictions on the import of various species. In addition, there was a growing demand for 'clean' animals, as we have seen at the RIVM.[74]

With the increased popularity of breeding programs came increased attention to reproduction in captivity and nursery care, as primates turned out to be notoriously hard to keep and breed in captivity.[75] Thus, the RIVM breeding program and others like it entailed a lot more than putting a male and a female monkey into a cage together and hoping for a baby. As we can read in reports from 'Project 13b: Development of Monkey Breeding Programs', started in 1978, a number of measures were taken and experimented with to 'improve conditions and procedures to get to an optimal production and supply of cynomolgus monkeys'.[76] This project in particular focused on measures improving the reproductive success of the breeding program. In 1979, a "final shipment" of 340 monkeys was acquired, enough for a year's worth of vaccine production and testing in 1980. The shipment included fifty female adult monkeys for breeding purposes because from that year on all monkeys used for testing were to be home-bred.[77]

For the Polio-monkeys, this meant increased human control over their lives. Their birth, housing, food, social interaction, reproduction, time, and cause of death were all largely (and literally) in the hands of RIVM staff. One reproductive measure was to track the menstrual cycles and pregnancy stages of all female monkeys through urine tests

70 Erwin et al., Captivity and Behavior.

71 Chris Herzfeld, Seven. Socialities, Culture, and Traditions Among Primates, The Great Apes (Yale University Press, 2017), pp. 201–36. <https://www.degruyter.com/document/doi/10.12987/9780300231656-010/html> [accessed 23 February 2021].

72 Ibidem.

73 Erwin et al., Captivity and Behavior.

74 J. Erwin, 'Factors Influencing Survival and Development of Macaca Nemestrina and Macaca Fascicularis Infants in a Harem Breeding Situation', in Nursery Care of Nonhuman Primates, ed. by Gerald C. Ruppenthal and Dorothy J. Reese, Advances in Primatology (Boston, MA: Springer US, 1979), pp. 239–52 <https://doi.org/10.1007/978-1-4684-3477-4_18>.

75 Erwin et al., Captivity and Behavior.

76 Project 13b: Ontwikkeling Apenkweek door R. Boot, oktober 1979-maart 1980 and march-october 1979, and nov. 1978-march 79. 78-80. RIVM Archive, file no. 1050042.

77 We will see later that it was not actually the last shipment. 'Project 13b: Ontwikkeling Apenkweek' by R. Boot, October 1979 - March 1980, March - October 1979, and November 1978–March 1979. RIVM Archive, file no.1050042.

and observations of bleeding.[78] This gave information on when to pair females with males but also on which pregnant females to pair together (as the intention was to house two females together who were going to give birth at approximately the same time). The researchers found that babies from two mother monkeys housed together were born in better physical condition than babies from females housed individually. The babies' better health made it possible to wean them at an earlier age, which improved breeding efficiency. For group housing, the composition of groups seemed to likewise have a strong effect on the loss-percentage of baby monkeys. More intensive contact with animal caretakers was thought to contribute to lower death rates.[79] One of the Project 13b reports indicated that not only physical health but also healthy behavior needed to be considered if optimal results were to be achieved in the breeding program.[80] In addition, a literature review found that the effects of breeding conditions on sexual potency were great, and it was thus concluded that raising monkeys in isolation from a very young age should be avoided. Still, losses of quite a number of baby monkeys turned out to be unavoidable.

Another reproductive measure that was experimented with is described in the document 'Recovery cycle after weaning, mating induction'. The babies of three macaques (numbered 6, 876, and 925) were weaned on January 1, 1979. Macaques 876 and 925 were paired with a male macaque between January 22 and January 26 and between February 5 and February 9 (in the second period only during the day). If bleeding occurred after the first mating period, humans conducted a daily vaginal flushing of the macaque with 0.2 cc of saline solution and collected the mucus on a clean glass plate. The second mating session was then planned based on the fern pattern, the appearance of which was thought to be indicative of rising estrogen levels. In addition, daily urine samples were collected throughout the experiment.[81]

The breeding program thus meant that monkeys and humans spent more time together and engaged in a larger variety of interactions—including more intimate physical contact both among monkeys and between monkeys and humans. This is therefore a good moment to zoom in on the micro-level of the lab and the embodied experiences of the monkeys and humans that were part of the polio vaccine practice. Pictures and interviews give us more information about these daily interspecies encounters and show that these nonhuman animals were not just materials to the human researchers. Rather, there was a tension between the monkey as material and the monkey as fellow living

78 Project 13b: Ontwikkeling Apenkweek door R. Boot, oktober 1979-maart 1980 and march-october 1979, and nov. 1978-march 79. 78-80. RIVM Archive, file no.1050042 Proefdiervoorziening 1970-1980. For a discussion of the 'genderedness' of the experiences of the Polio-monkeys, see: Anne van Veen, Breeding Ladies. In Women in the History of Science: A Liberating the Curriculum Sourcebook, edited by R. Martin, F. Lawrence-Mackey, S. Harrison, E. Jone, and H. Wills (London: University College London Press, forthcoming in 2021). For more on gendered dualisms in menstrual science in general, see: Catherine Duxbury, 'Of Monkeys, Men and Menstruation: Gendered Dualisms and the Absent Referent in Mid-Twentieth Century British Menstrual Science', Journal of Historical Sociology, 32.1 (2019), 94–107 <https://doi.org/10.1111/johs.12218>.

79 Project report 94.83.02/13.01.01 Monkey Breeding by R. Boot on 2/3/1981. RIVM Archive, file no. 1050041.

80 Project 13b: Ontwikkeling Apenkweek door R. Boot, oktober 1979-maart 1980 and march-october 1979, and nov. 1978-march 79. 78-80. RIVM Archive, file no. 1050042.

81 Herstel cyclus na spenen; paringsinduktie. 29/01/1979. A. Kamer/F vd Sluijs, Dr. LG Huis in 't Veld, BC Kruijt, R. Boot. RIVM Archive, file no. 1050042.

being, or, seen from the monkeys' perspective, a tension between humans as threats/captors and caretakers (in some instances even parents).

Ethnographic research by Arluke has shown that within the laboratory space, nonhuman animals are not continuously objectified, but rather move back and forth between being "pet" and object through processes of anthropomorphizing and counter-anthropomorphizing.[82] This can be understood as a way in which humans deal with the psychological demands of the job. While objectification makes killing (or "sacrificing") the lab animals easier, anthropomorphizing is a way for humans to deal with the empathy they feel for the lab animals. According to Arluke, objectification is facilitated by de-individualization, hence the common practice of giving tested animals numbers instead of names. This de-individualization occurs more easily in 'lower' animals that are handled in large 'batches' instead of individually. Nonhuman animals that spend a long time in the lab are more likely to be named and names are most likely to be used by those who spend substantial time with conscious nonhuman animals, such as ATs and caretakers. From the outset of the breeding program at the RIVM, this de-individualization became increasingly difficult. Not only were there a lot fewer monkeys that lived much longer before being killed, successful breeding required paying more concentrated attention to individual macaques to ensure successful reproduction. Macaques were now being born at the RIVM, where they would spend the first six months of their lives with their mothers. Some orphaned or rejected macaque-babies were hand reared by human caretakers and/or adopted by a female macaque. After weaning, they would continue to live for another year on average, before being old enough (i.e., their kidneys large enough) to be killed.

Although standard practice at the RIVM was not to name any lab animals, some exceptions were made. In the archives, monkeys and other lab animals are regularly referred to as materials and always referred to by number. Yet some challenges to this discourse can be found as well. A handwritten document about a group of wild-caught monkeys brought in in 1990 said: 'Monkey 4139 started to clearly lose weight because of homesickness after his cage mate had been removed'.[83] Clearly, Monkey 4139 was at that moment of observation not seen as material, but as a fellow living being that could be empathized with. Young monkeys were also referred to as children in one document, and adults were sometimes discussed as men, women, and mothers.[84] In the pictures in the image bank, the monkey as fellow living being and the human as caretaker are more clearly visible. There are pictures of humans and monkeys in friendly interaction and play, angry monkeys, cuddling monkeys, humans teasing monkeys, the hand-rearing of monkeys, etc. According to Irvine, play between human and nonhuman animals can be seen as micro-challenges to a human/animal dichotomy since play '[…] honors animals' subjectivity and communication skills, making this everyday activity an act of individualized resistance to human disregard for non-human life'.[85] In a similar vein, macaques biting humans when they did not want to be caught can also be seen as

82 Arnold B. Arluke, 'Sacrificial Symbolism in Animal Experimentation: Object or Pet?', Anthrozoös,, 2.2 (1988), 98–117 <https://doi.org/10.2752/089279389787058091>.

83 Author unknown (n.d.), handwritten note in file 'Purchase of wild-caught monkeys'. RIVM Archive, file no. 24035.

84 For example: Drs. Lidia van Huizen: Rapportage Polyoma in Polio-pool volgens Kepner Tregne Probleem Analyse methode, p.3. 1998. RIVM Archive, file no. 1049522.

85 Leslie Irvine, 'The Power of Play', Anthrozoös, 14.3 (2001), 151–60 <https://doi.org/10.2752/089279301786999454>, 1.

micro-challenges, in which macaques try to resist human domination over their lives, showing themselves to be subjects rather than objects alone.

There are also many pictures of the monkeys' kidneys after they had been removed from the monkeys. In contrast, among the seventy-six monkey pictures, I found only two pictures depicting 'monkeys as materials': a monkey undergoing safety testing and a monkey being prepared for kidney removal.

Figure 3.6 Agitated monkey. Source: RIVM.

Figure 3.7 Monkey on the roof. Source: RIVM.

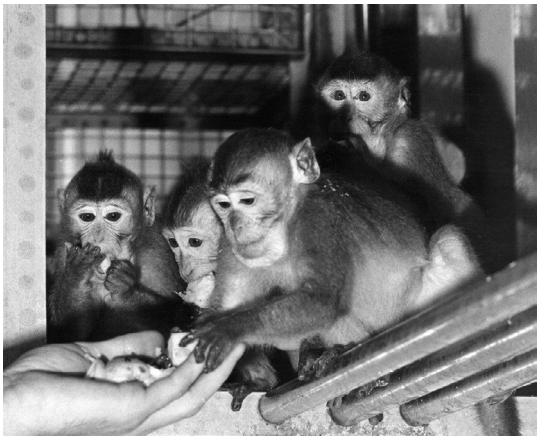

Figure 3.8 Hand-feeding monkeys. Source: RIVM.

It is important to note here that affection is not the opposite of domination. In fact, affection is often what makes domination possible. As one AT put it: 'You have to care about animals if you want to be able to do this job', but also 'you have to be able to flip a switch [in your head] and see the animal as an object'.[86] The affection felt for (certain) monkeys becomes clear when looking at the types of pictures that were taken and saved to the image bank, which demonstrate a clear preference for pictures which depict monkeys as (cute) living beings.

I observed something similar in an interview with one of the ATs who worked with the monkeys for a long time.[87] He was very happy to show me pictures of the monkeys and tell stories about them but preferred not to dwell on their deaths or look at the more gruesome pictures of their actual use in polio vaccine production. When I asked if it was difficult to kill the monkeys, he answered that one knows that it is part of the job, 'they are not pets'. This classification or labelling of animals according to their function is another means of facilitating objectification.[88] By saying that the macaques are not pets, the AT drew a boundary between groups of animals—not based on their species but on their intended use by humans—which in turn made it easier to accept that they had to be killed.

As reluctant as he was to talk about killing the monkeys, he was eager to share a story which revolved around caring for a baby macaque. This young macaque had lost his mother on a Friday and was too young to live without maternal care. Given that it was impossible to arrange care at the RIVM for the weekend, this AT took the monkey home to take care for him. The following Monday the young macaque was given to another monkey who had a baby the same age. She was 'very eager' to adopt him.

Another story involved two young monkeys, who were rejected by their mothers. They were hand-reared by ATs, who named them Fred and Christ. In addition, an artificial 'surrogate mom' (Figure 3.10), which was placed in their cage. Later, they were adopted by a female monkey.[89] These stories and images demonstrate how monkeys could assert themselves as living beings in their interaction with humans. They challenged objectification by escaping, becoming angry or biting, but also by being 'cute' and thereby eliciting an empathetic reaction in humans.

These stories and images also demonstrate how relations of care were part of day-to-day life in the lab and reminds us that the monkeys were never *just* 'lab monkeys' but also formed relationships with one another as mothers, fathers, children, friends, enemies, et cetera. Despite these routine non-instrumental interactions between humans and monkeys, the final interaction would be the same for all monkeys. How then did the 'laboratory choreography' end for an RIVM Polio-monkey? A macaque of about eighteen months old would be captured in her cage, fully anaesthetized, and moved to an operating room.[90] There, her aorta and *arteria mesenterica* were clamped and her kidneys were perfused at a low pressure with a trypsin solution of 300–500 ml. This took 15–20 minutes. When the perfusion was complete, her kidneys were removed aseptically, and the monkey was killed and 'disposed of'.

86 Interview R3.

87 Interview R2.

88 Arluke, Sacrificial Symbolism, 101.

89 Interview R2.

90 G. van Steenis and others, 'Use of Captive-Bred Monkeys for Vaccine Production.', Developments in Biological Standardization, 45 (1980), 99–105. Eighteen months was the mean age, but killing ages varied from eight to thirty-five months.

Figure 3.9 Bottle feeding. Source: RIVM.

Figure 3.10 Fred and Chris with their 'surrogate mother'. Source: RIVM.

Figure 3.11 Fred and Chris. Source: RIVM.

Figure 3.12 Animal technician preparing food. Source: RIVM.

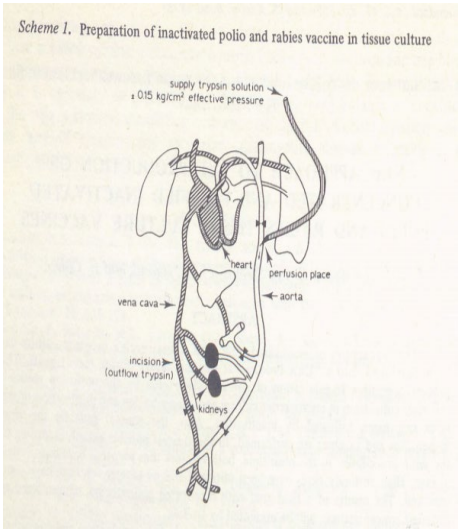

Figure 3.13 Schematic of the perfusion process[91]

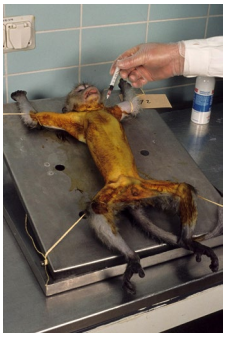

Figure 3.14 Monkey under general anesthetic. Source: RIVM.

Figure 3.15 Jars with monkey kidneys. Source: RIVM.

Figure 3.14 is one of the few pictures in the image bank of a monkey actually being tested on. Several (former) RIVM employees commented on how a picture such as this

91 Source: Van Wezel et al., New Approach, 160.

one would not be very nice to show, expressing a preference for pictures of living monkeys or something more schematic like the figure on the left. This preference was not only about preferring to see living monkeys over dead ones, but also about protecting the reputation of the RIVM and being concerned that animal rights activists might (ab) use the pictures. Despite the fact that there are no longer monkeys at the RIVM, concerns still emerged that pictures of dead monkeys could fall into the 'wrong' hands and be used to damage the RIVM's reputation or even threaten the safety of employees.

We have seen that, although their deaths ultimately remained the same, the breeding program had a large impact on the daily lives of the RIVM monkeys. In the next section, we will consider two other developments that affected the use of monkeys for polio vaccine production and control: the Animal Testing Act of 1977 and the increased focus on the 3Rs in nonhuman animal testing.

3.6 THE ANIMAL TESTING ACT, 3RS, AND THE POLIO VACCINE

While ethical concerns about nonhuman animal testing and monkey use more specifically were not prominent issues in earlier periods, this would change in the 1980s: the period of nonhuman animal testing legislation, the 3Rs, and animal rights activism (see Chapter 2). As we have seen, the number of monkeys being used for testing reduced dramatically before 1980. The reduction was driven not by ethical concerns over the use of animals but rather by monkey scarcity, economic reasons, and safety issues. In the 1980s, 'ethics' entered into the discourse, though, as we will see, a number of additional reasons played into the application (or non-application) of the 3Rs as well. I will first consider the new animal testing law of 1977 and what this meant for the use of monkeys and the polio vaccine. Secondly, I will look at how welfare and housing measures 'refined' monkeys' lives and what happened when these refinement measures conflicted with human interests, such as efficiency and risk aversion. Thirdly, I consider the Vero cells as a potential in vitro replacement for the polio vaccine. I conclude with a discussion of a protest against the RIVM's use of monkeys.

3.6.1 The Animal Testing Act

The first Animal Testing Act in the Netherlands was passed in 1977 and enacted in the years that followed. The 1980 RIVM report on 'developments in lab animal supply' discussed the new law, noting the two most important elements to be: 1. It is forbidden to test on animals when an alternative is available; 2. It is forbidden to test on a horse, monkey, dog, or cat if the same can be achieved using a different animal species. At the RIVM, this new law was not considered problematic, as it was in line with existing RIVM policy and would not require any major changes.[92]

The law's favoring of monkeys over most other nonhuman animals reflected changing societal attitudes towards nonhuman primates. As humans became more aware of the similarities between themselves and other primates, they also became more opposed to using them in experiments. As Midgley puts it, 'If they are sufficiently like us to be really comparable, they may be too like us to be used freely as experimental sub-

92 'Proefdiervoorziening: kweekmethoden' by B.C. Kruijt en R. Boot, March - October 1980. RIVM Archive, file no. 1050042.

jects'.[93] The legal favoring of nonhuman animals 'like us' as well as nonhuman animals 'we like' (i.e. species seen as 'pets') created a hierarchy of species that Dunayer refers to as 'new-speciesist'.[94] Dunayer distinguishes between old-speciesism and new-speciesism, where old-speciesism placed humans above all other animals but did not distinguish between nonhuman animal species. New-speciesism, in contrast, advocated for extending legal rights beyond humans and giving human-like animals more rights than other animals. Although the Animal Testing Act distinguished between species and gave more protection to human-like nonhuman animals than other nonhuman animals, all nonhuman animals remained devoid of any legal rights.

The policy of replacing 'higher' animals with 'lower' animals in testing, was especially relevant in the case of the polio vaccine, since this was one of the few purposes for which the RIVM used monkeys. In an abstract, we can read: 'For ethical reasons and also in view of the increasing scarcity of monkeys, attempts were made to reduce the number of monkeys [...]' and 'significant reductions were achieved by [...] 3. Replacement of monkeys by rats in potency testing of vaccines'.[95] Notice first how, suddenly, 'ethical reasons' have been given as the main justification for reducing monkey use, in contrast to earlier articles which only mentioned monkey shortages, costs, safety, and independence from foreign sources. The second significant moment is in point three, where the text states that by replacing monkeys with rats a reduction in monkey use has been achieved. This also, of course, would have achieved an increase in the number of rats used. Here we see that replacing monkeys with rats was understood as something self-evidently ethical; it was better to use rats than monkeys and this required no further explanation. In an interview, R4, a long-term employee working in the polio lab, reflected on this difference between species. He explained that although the reduction of testing on nonhuman animals (across species) had always been the goal, one could not help but feel more affected when seeing monkeys being tested on, as they were so similar to human children.[96] This sentiment can also be observed in the protests of (some) animal rights activists, who tended to focus their protests more on primates, cats, and dogs than on 'lower' animals (although this may also have been for strategic reasons, given that experiments on these species were thought to affect the general public more, see Section 3.6.4).

The rats and mice used in polio testing were not just any rats and mice, but rather creatures specially created for scientific purposes. Even more so than monkeys, strains of mice and rats were adapted to being research instruments; they were purposely created for science, thereby becoming a 'laboratory animal species'. In 1981, Steenis el al. published an article about the experiment that made it possible to replace monkeys with rats in potency testing. According to the article, this replacement was motivated by a lack of quantitative data obtained in the monkey test and '[...] because monkeys are becoming scarce and too expensive for this type of testing'.[97] Therefore they '[...]

93 Mary Midgley, The Myths We Live By (Florence, UNITED STATES: Taylor & Francis Group, 2003), 147.

94 Dunayer, Speciesism.

95 G. van Steenis, A.L. van Wezel and R. Boot, 'Reduction in number of monkeys needed for poliomyelitis vaccine production', ZEITSCHRIFT FUR VERSUCHSTIERKUNDE (GUSTAV FISCHER VERLAG JENA VILLENGANG 2, D-07745 JENA, GERMANY, 1982), xxiv, 61–62.

96 Interview R4.

97 G. van Steenis, A. L. van Wezel, and V. M. Sekhuis, 'Potency Testing of Killed Polio Vaccine in Rats', Developments in Biological Standardization, 47 (1981), 119–28, 119.

examined whether one of the small *laboratory animal species* could satisfactorily replace the monkey for this purpose'.[98] The 'laboratory animal species' which were tried out were outbred guinea pigs, outbred SPF-Wistar rats, outbred SPF Swiss NIH mice, inbred rats, and inbred mice. The rat was selected because it was a good model for 'man', cheap, and of practical size.[99] Here we see a very different motivation for replacing monkeys with rats, one not based on ethics. This is more in line with what we saw in the previous section; the arguments which Lansberg gave in 1975 to keep the monkey test and that van Steenis gave to stop using 'expensive' monkeys indicated that, at that stage, a new-speciesist ethic favoring monkeys over rats was not yet the main driver for replacing monkeys with rats. It seems likely that the 1982 poster abstract may have reconstructed these replacements as ethically motivated in order to fit with the by then increasingly popular 3Rs discourse.

3.6.2 Housing and Well-being

Since the monkeys were never willing participants in these polio practices, humans held them in cages to prevent them from leaving. At the RIVM, cages were also a way of keeping monkeys 'clean', by isolating them from other animals and separating different groups of monkeys. The production and control lines of monkeys were kept completely separate.[100] Young monkeys meant for production were weaned at five or six months and subsequently housed separately from breeding monkeys.

Growing concern for the welfare of nonhuman primates used for testing came not only from animal advocates and the public, but also from researchers themselves. In 1979, the Veterinary Head of Inspection (VHI) ordered a report to be written about the housing of monkeys, specifically macaques. The reason given for this was increasing concern from both researchers and animal protectors about macaques suffering in captivity.[101] One of the authors of the report was R. Boot, a researcher at the RIVM. An article was published based on this report which recommend housing macaques in groups because individual housing was causing abnormal behavior.[102] The recommended cage size was a minimum 0.7 square meters per monkey, with a recommended height of at least two meters. Perches were to be installed at different heights and at a short distance from the wall to leave room for the macaques' long tails.

The article gave other reasons for improving housing conditions in addition to concern over monkey suffering and monkey well-being. It argued that paying attention to the housing of the monkeys was important due to the influence this had on their capacity to reproduce, which was of course essential for a successful breeding program.

In the 1980s, the RIVM also conducted research which examined cage-preferences and the effects of housing conditions on pregnancy outcomes.[103] The research showed a

98 Emphasis mine. Ibidem, 119.

99 Both inbred and outbred rat lines gave the desired results. Ibidem.

100 Bespreking vervanging primaire apeniercellen voor controle doeleinden en diagnostiek, d.d.23/09/1980. RIVM Archive, file no.1016956.

101 Veterinaire Hoofdinspectie van de Volksgezondheid. Sectie Dierproeven., Zo doende 1982: jaaroverzicht door de Sectie dierproeven van de Veterinaire Hoofdinspectie van de Volksgezondheid, 1982.

102 C. Goosen and others, 'Recommendations for the Housing of Macaque Monkeys', Laboratory Animals, 18.2 (1984), 99–102.

103 Goosen et al., Recommendations; R. Boot, A. van Arnhem, and K. Pots, 'Kooipreferentie Bij Individuele Huisvesting van Java-Apen. 1e Interim Rapport', RIVM Rapport 948473001, 1988; Boot R and Staal J, 'Kooipre-

large variation in individual preferences among monkeys and stronger preferences for certain neighbors than for cage characteristics (although a corner perch was found to be popular). Pregnant monkeys were found to be more likely to give birth successfully in larger cages than in smaller cages. Although the well-being of monkeys had already been important for humans, since stressed monkeys meant decreased reproduction and increased costs, well-being seemed to become a goal in and of itself during the 1980s. The reports on housing preference tests, for example, explained the need for these experiments by stating that housing condition were thought to have an important effect on nonhuman animal well-being, without making any further references to the instrumental importance of this well-being.

Despite this increased attention on refinement for improving monkey welfare, the RIVM was not always in compliance with their own recommendations to house monkeys in groups. The preference for group housing for reasons of well-being and reproductive success sometimes conflicted with the preference for 'clean' monkeys, as diseases spread more easily in groups. Aggressive interactions also justified opting for individual housing. Because of this, the monkeys were transferred back and forth between group housing, individual or duo housing, or a combination of both. Just three years after the start of the breeding programs in harem groups, four of the twelve groups were cancelled due to problems with aggressive interactions. The monkeys involved became part of an individual breeding program. Within the individual breeding program, duo housing was experimented with to meet social contact needs. This had the added benefit of making the cages 'less uncomfortable' (size of 60 x 60 x 120 cm instead of 45 x 45 x 60 cm). Experiences were positive, but budget and space limitations did not allow implementing duo housing on a larger scale.[104]

Between 1986 and 1990, a switch was made from group housing back to individual/duo housing because of problems with Foamy virus.[105] When the number of females used for breeding was reduced, it became possible to house monkeys in larger cages (which was requested by the Head of Veterinary Inspection).[106] In 1989, there were ninety-four breeding monkeys and twenty-seven young monkeys 'in stock' for production.[107] In 1992, the RIVM started group housing back up again; to prevent further infections, they created Foamy virus negative groups. In 1988, the institute made the decision to stop the breeding program, because a switch to in vitro production of the polio vaccine was expected to start soon (see Section 3.5.3). This suspension turned out to be premature and the program started up again shortly afterward. During this period, many young females did not accept their young, which led to the babies being hand-

fentie bij individuele huisvesting van Java-apen tweede interimrapport', 1989 <https://rivm.openrepository.com/handle/10029/262181> [accessed 24 February 2021].

104 Project report 13 01 01 Monkey breeding by R. Boot on 29/10/1982. RIVM Archive, file no. 1050041.

105 Foamy viruses are retroviruses that naturally occur in nonhuman primates. They are mainly transmitted through saliva and are non-pathogenic but may cause increased morbidity of other pathogens. Delia M. Pinto-Santini, Carolyn R. Stenbak, and Maxine L. Linial, 'Foamy Virus Zoonotic Infections', Retrovirology, 14.1 (2017), 55 <https://doi.org/10.1186/s12977-017-0379-9>.

106 Project Apenkweek 13.01.01 by Drs. R. Boot report 11/1985-11/1986 (18/11/1986). RIVM Archive, file no. 1050041.

107 Document 'Situatie omtrent de bij het RIVM aanwezige kolonies cynomolgus apen ten behoeve van de bereiding van IPV. 12/6/1989. RIVM Archive, file no. 1049522.

raised— providing an ideal starting point for Foamy virus free groups.[108] Foamy virus positive monkeys were still housed individually for some time until, in 1997, they were re-socialized into group housing 'under pressure from animal welfare legislation'. [109]

Figure 3.16 Group housing with refinement. Source: RIVM.

Figure 3.17 Larger individual or duo cages. Source: RIVM.

The picture on the left shows that the monkeys' living conditions were also refined by adding toys to their cages. While still living in the small cages, they were sometimes let out to stretch their legs.

3.6.3 In Vitro Alternative: the Vero cell line

Since the 1960s, cell lines had been mentioned as a possible alternative for monkey kidney cells as a substrate for the production of the polio vaccine. The Vero cell line was first created in 1962 by Y. Yasumura and Y. Kawakita at the Chiba University in Japan.[110] It was derived from the kidney cells of a healthy African green monkey and

108 Rapportage polyoma problematiek, 27/11/1998 P. de Vrey, CDL Ch. Jansen van 't Land MKB. RIVM Archive, file no. 1049522.

109 Plan van aanpak Polyoma-problematiek, C. Janssen van 't Land, 1999. RIVM Archive, file no. 1049522.

110 Rebecca Sheets, 'History and Characterization of the Vero Cell Line', Cent Biol Eval Res (CBER), 2000, 1–12.

Figure 3.18 Older, smaller cage. Source: RIVM.

the cell line was continuous, meaning that it would grow indefinitely in culture. Cell banks were established for worldwide distribution of the Vero cell line.[111] The Merieux Institute in France began producing Vero-IPV in 1982 and collaborated with the RIVM in developing the vaccine.[112] The WHO established requirements for using continuous cell lines for IPV production in 1980 and by the time the RIVM applied for licensing of Vero-IPV the vaccine had already been licensed in sixty countries.[113] We saw earlier that the 3Rs had become more important and that acceptance of using nonhuman primates in research was decreasing. Considering all of this, one wonders why it took so long (and *could* take so long) to make the switch to the Vero-IPV.

It is not at all the case that the RIVM had no interest in using Vero cells. In the early 1980s, researchers at both the RIVM and the Merieux Institute were optimistic about switching to the continuous cell line in the near future.[114] In 1981, Van Wezel wrote to Montagnon at the Merieux Institute about the Vero-IPV vaccine: 'I do not expect many problems [in getting] this vaccine generally accepted'.[115] In fact, RIVM researchers pre-

Vero is an abbreviation of VErda RenO (green kidney) as the cell line is derived from kidney cells of an African green monkey.

111 Sheets, History and Characterization.

112 B. J. Montagnon and J. C. Vincent-Falquet, 'Experience with the Vero Cell Line.', Developments in Biological Standardization, 93 (1998), 119–23.

113 Inactivated Poliomyelitis vaccine. Part IC1: Chemical pharmaceutical expert statement. April 2003. RIVM Archive, file no. 1059292.

114 For example: Brief van Ir. A. L. van Wezel aan Dr. G. van Steenis, Betreft: controle poliovaccin geproduceerd op Vero-cellen. 3/05/1983. RIVM Archive, file no. 1050067 Vaccin ontwikkeling 1970-1984, The Vero cell line is mentioned in every yearly vaccine development report in this file from 1980 onwards.

115 Letter from A.L. van Wezel to Dr. B. Montangon on 2/6/1981. RIVM Archive, file no. 1017278

dicted throughout the 1980s and 1990s that 'soon', monkeys would no longer be used. In 1983, they prepared the first batches of the vaccine on Vero cells, which were tested in 1984 for potency and safety.[116]

In 1984, Bernard J. Montagnon, head of Virology Production at Merieux, wrote an article about the use of Vero cells at the Merieux Institute, in which he described the importance of RIVM researchers for the development of this newest IPV vaccine.[117] Indeed, the RIVM contributed to the French Vero-IPV in various ways. The preliminary results of the Vero-IPV were presented in June 1980 in Bilthoven at the International Symposium on Reassessment of Inactivated Poliomyelitis Vaccine. The cells had been grown using Van Wezel's microcarriers and Van Heemert's Bilthoven Unit and the test for tumorgenicity had been described by Van Steenis and Van Weezel in 1982. The newborn rats used for control tests at Merieux were immunodepressed with antithymocyte serum (ATS), a formulation originally prepared by Van Steenis at the RIVM following the procedure of RIVM-researcher J.G. Kreeftenberg. According to interviewee R4, Merieux always gave RIVM researchers the credit they were due.[118]

Despite these close collaborations, scientists at the RIVM were still concerned about the risks involved with using the continuous cell line. There were two safety concerns with the Vero cell line at that time: tumorigenicity and residual cellular DNA/RNA, which needed to be removed as much as possible in the purification process in order to be below a safe limit. In the early 1980s, it was already clear that tumorigenicity would not be a problem and tests for residual DNA/RNA showed that they were well below the accepted limit. The potency of the vaccine was also fine, comparable to that of the vaccine prepared on monkey kidney cells.[119] Yet more tests were needed to quell concerns about possible long-term effects.[120]

Despite optimism about the Vero cell line, some indications suggest that given the successes with the subcultivation of monkey kidney cells, which dramatically reduced the need for monkeys, the urgency around shifting methods may have been somewhat subdued. In 1979, cells from a continuous cell line received from the Salk Institute were frozen: 'because of the shortage of monkeys, the research on the preparation of IPV on secondary (or tertiary) kidney cells from own bred monkeys has priority now. The results are very promising'.[121] A report from March 1984 stated that 'there is no necessity to change the control/production system short term'.[122] Moreover, in a chapter on cell substrates from the early 1980s, Van Wezel et al. wrote that they thought more research on tumorigenicity and residual DNA was needed before implementing the Vero cell line. In the meantime, subcultured monkey kidney cells were regarded as an excel-

116 Yearly report Project 02.01 - Poliomyelitisvaccin (geinactiveerd) - Bereiding written by Van Wezel, 1983, 1984, 1985. RIVM Archive, file no. 1017133.

117 B. J. Montagnon, B. Fanget, and J. C. Vincent-Falquet, 'Industrial-Scale Production of Inactivated Poliovirus Vaccine Prepared by Culture of Vero Cells on Microcarrier', Reviews of Infectious Diseases, 6. Supplement 2 (1984), S341–44.

118 Interview R4.

119 Yearly report Project 02.01 - Poliomyelitisvaccin (geinactiveerd) - Bereiding written by van Wezel, 1983, 1984, 1985. RIVM Archive, file no. 1017133.

120 Interview R4.

121 Letter from A.L. van Wezel to dr. Jonas Salk on april 3, 1979. RIVM Archive, file no. 1016835

122 U 99/84 LGV Ma/kdf Dr. Beuvary (et al) Aan Dr. J. Freudenthal. 01/03/1984. RIVM Archive, file no.1017133.

lent alternative for primary cells as far as production of IPV for the National Vaccination Program (RVP) in the Netherlands was concerned. For worldwide production of IPV, however, the use of continuous cell lines was thought to be required for economical and practical reasons.[123]

R4, who worked in polio vaccine production for a long time, mentioned similar reasons for delaying the switch to Vero-IPV.[124] He explained that using continuous cell lines was at that time an extremely sensitive subject, despite test results indicating the safety of its use. There was a great deal of fear regarding the tumorigenicity of the cell line, and there was no real need to change the production process. Since only a few monkeys were used for the National Vaccination Program, thanks to the improvements made to the efficiency of the Unit Process, money use did not pose a problem. He speculated that the Merieux Institute was less concerned about possible public health risks because it was a commercial institute and had different interests from the RIVM (whose main interest as a government institution was to protect the Dutch people and not take any risks with their health). Then, as now, risk aversion is found to be one of the major barriers to implementing alternatives.[125] In analyzing cases of transitions towards alternatives, Schiffelers found that researchers were aware of both the public demand for risk minimization and the public demand for less nonuhman animal testing, yet the demand for risk minimization was perceived as greater.[126]

Meanwhile, Jonas Salk was still dreaming of, and trying to work towards, global use of IPV. As mentioned previously, a major obstacle to worldwide implementation of an IPV vaccination was its higher cost compared to OPV. Since using a cell line was much cheaper than using monkeys, it should come as no surprise that Salk was enthusiastic about the prospects of producing IPV without the use of monkeys. On August 29, 1980, he wrote to Dr. V Ramalingaswami, Director General of the Indian Council of Medical Research, that the Merieux Institute was making progress with large scale Vero-IPV, which would obviate the need for monkeys and make costs no longer a barrier when considering the use of IPV. 'If, as seems likely, KPV [IPV] proves to be of value under the circumstances that prevail in India, it would be desirable to give consideration soon to establishing a capability for production of KPV in India not only for use domestically, but for export as well'.[127] Despite these new developments removing the cost-barrier of IPV, the world did not immediately switch to IPV in the early 1980s. Salk remained hopeful, however, as we can see in his 1986 letter to Jianng Shude who was going to spend a few months at the RIVM and the Merieux Institute (financed by FAIR): 'The polio vaccine story is not yet over. I am sure that there is a better way to solve the problem than is currently practiced'.[128]

At the RIVM, continuous cell lines continued to be a topic of interest in the late 1980s

123 Chapter 3: Cell Substrates by AL van Wezel, R. Boot, G. van Steenis, and CAM van der Velden-De Groot. n.d. RIVM Archive, file no. 1017223.

124 Interview R4.

125 J. T. de Cock Buning and others, 'Maatschappelijke trendanalyse dierproeven 2009 deel A en deel B.', 2009 <https://research.vu.nl/en/publications/maatschappelijke-trendanalyse-dierproeven-2009-deel-a-en-deel-b> [accessed 24 February 2021]; M. J. W. A. Schiffelers, 'Animal Testing, 3R Models and Regulatory Acceptance : Technology Transition in a Risk-Averse Context', 2016 <http://dspace.library.uu.nl/handle/1874/334103>.

126 Schiffelers, Animal Testing.

127 Letter from J. Salk to V. Ramalingaswami on 29/08/1980, 2. RIVM Archive, file no. 2152 9A2-5.

128 Letter from Jonas Salk to Jianng Shude 3/6/1986. RIVM archive, file no 1017053.

and 1990s. In 1988, the expectations regarding Vero-IPV were so high that the breeding of monkeys was stopped, and the surplus was sold to institutes in Germany and Scandinavia.[129] This proved a bit too optimistic however and, in 1990, the RIVM bought thirty-one wild-caught monkeys from the commercial supplier Hartelust in Tilburg and a few more captive-bred monkeys from Charles-River to deal with an acute monkey shortage. The Animal Experiments Committee (AEC) of the RIVM expressed concern about these developments, especially the consequences of capture and transportation and then keeping the wild monkeys in captivity (indeed 30% of these monkeys died upon or shortly after arrival). They urged the RIVM to prevent this in the future by creating clarity about the need for monkeys in the coming years. They also emphasized the great value of the possibilities of continuous cell lines.[130] As R4 put it: 'The AEC really kept pushing it'.[131]

In 1989, researchers were urged again to come up with a proposal for developing Vero-IPV. This time, the encouragement came from one of their RIVM colleagues, M. Krasselt, not for reasons of animal welfare but due to a safety concern (a cytopathic effect indicating a virus infection that had been found in cell cultures from monkey kidney cells).[132] It was again estimated that the transition would take several years, probably five to seven.[133]

3.6.4 Protest

While researchers and policy makers focused on the 3Rs, animal rights activists had a different ethical view in which testing on nonhuman animals, and especially primates, was seen as morally wrong in all circumstances. This included the RIVM's use of macaques for the polio vaccine. Although the RIVM was not frequently targeted by activists, occasional peaceful protests did occur. On Monday, April 24, 1994[134], around lunch time, two buses arrived at the RIVM in Bilthoven.[135] The buses held protesters participating in the 'Amnesty for Monkeys' campaign, a joint action between the NBBV and Proefdiervrij. Together with monkey-mascots named Gino and Gina, they demanded the release of all monkeys. Realizing this would not happen immediately, they formulated three further demands in a letter to RIVM director Kroes.[136] First, they asked for a statement in which institutes declared that they would abstain from importing wild monkeys. Second, they asked the RIVM to join a new reduction committee, which was going to develop a program for reducing and eventually abolishing all monkey use in

129 Letter from drs. P. de Vrey to ir. drs. RBJC van Noort, regarding the DEC letter from 4/5/1991 (no date). RIVM Archive, file no. 24035.

130 Letter from Dr. GJA Speyers and Dr. CFM Hendriksen of the DEC to Ir. Drs. RBJC van Noort (RIVM) on 5/4/1991 regarding acquiring wild caught monkeys. RIVM Archive, file no. 24035.

131 Interview R4.

132 Document 'Situatie omtrent de bij het RIVM aanwezige kolonies cynomolgus apen ten behoeve van de bereiding van IPV. 12/6/1989. M. Krasselt. RIVM Archive, file no. 24035.

133 A possible difficulty mentioned was that the Merieux Institute had a patent on using Vero cells for IPV, so a license would have to be negotiated. Later it turned out, however, that the patent could be circumvented because it was connected to the use of a specific type of fermenter, which the RIVM did not use. RIVM Archive, file no. 24035; interview R4.

134 April 24 is World Lab Animal Day.

135 Proefdiervrij, Ledenblad 2, Den Haaf, 1995. Proefdiervrij Archive.

136 Letter from M. Zuidgeest to Mr. Kroes, 21/2/1995, The Hague. Proefdiervrij Archive.

research. Finally, they asked for the improvement of monkey housing conditions. The RIVM was willing to enter into dialogue with the protesters (in contrast to some other institutes that were being visited) and the action groups rewarded them for this with a 'toy and snack package' for the monkeys (figure 3.18). According to Kroes, they had an honest conversation: 'Critical groups keep us researchers alert. It makes [us] keep looking for alternatives'.[137]

The Amnesty for Monkeys' position was that monkeys should be released immediately, regardless of consequences for humans. Acting as advocates for the monkeys, they tried to establish an alternative discourse in which nonhuman animals were not resources for human use. Recognizing their subordinate position and limited power to change the hierarchy of discourses immediately, they chose to be pragmatic and also focused on the 'alternatives' discourse, as this might have been more effective in the short term.[138] As we will see next, however, it would still be over a decade before monkey use ended.

Figure 3.19 Protesters hand over toy and snack package for the monkeys. Source: RIVM.

3.7 THE LAST MACAQUE

By 1991, the development of Vero-IPV was listed as one of the five most important R&D projects at the RIVM.[139] There were several reasons for the switch to Vero-IPV becom-

137 Brabants dagblad, 25-04-1995, by Hans Rube. Proefdiervrij Archives.

138 For a more elaborate discussion of the protest, see: Anne van Veen, 'De Muis van Troje', Ex Tempore, 37.3 (2018), 244–57.

139 Document 'Beoordeling van de belangrijkste potentiële RIVM ontwikkelingsprojecten van biologische produkten', RIVM 1991. RIVM Archive, file no. 24035.

ing more and more important. Firstly, there was an increase in monkey use as more and more vaccine was produced for export. While the National Vaccine Program (RVP) could be serviced with only five to six monkeys, export needs were requiring thirty to forty monkeys per year by the late 1990s.[140] RIVM set up these IPV export programs to generate income, which they used to finance their GMP (Good Manufacturing Practices) investment program between 1987 and 1997.[141]

Secondly, there was a problem with polyomavirus. In the 1990s, monkeys were regularly found to be infected with polyomavirus and, in 2002, forty-five of the eighty monkeys at the RIVM were polyoma positive.[142] Since these polyoma positive monkeys could not be used to produce the polio vaccine, there was renewed threat of a monkey shortage. Buying new monkeys was considered as a solution, but this option was dismissed because it would have been very hard to find monkeys that met the strict registration requirements. Indeed, even if they had been found, no airline would have been willing to transport them.[143] An alternative solution was to import monkey-kidneys instead of monkeys, and this was approved as a viable option. The main message, however, was to hurry up with Vero-IPV registration.[144]

Thirdly, producing Monkey Kidney IPV (MK-IPV) had become an economic risk, since it was unknown whether or not there would still be an export market for it with the impending switch to Vero-IPV.[145]

Lastly, Vero-IPV had some important safety advantages over MK-IPV; the cell-lines could be controlled better than monkeys reducing the risk of contamination.[146] By the early 2000s, there was also such overwhelming evidence from long-term and large-scale use in other countries, that risk aversion was no longer a barrier. Altogether, it could no longer be claimed that these monkeys were *needed*, which delegitimized using them as a resource to produce the polio vaccine. Plans were made to make the switch to the IPV as quickly as possible, which required the registration of Vero-IPV not only in the Netherlands but also in all the countries to which the RIVM was exporting. The last time a monkey's kidneys were perfused and removed in Bilthoven was on December 22, 2005.[147]

Instead of completely closing the monkey colony at that point, the NVI kept a few cynomolgus monkeys. They did so because they expected that there would be an increased need for them for what they called 'emerging infections'.[148] In the document

140 Email 'Plan van aanpak Polyoma-problematiek' van Prof. dr. BAM van der Zeijst aan Mw. C. Jansen van 't Land op 24/6/1999. RIVM Archive, file no. 1059290.

141 Projectplan Uitplaatsing LVP naar de SVM Stichting tot bevordering van de Volksgezondheid en Milieuhygiene. October 1997. RIVM Archive, file no. 24035.

142 Bijlage DO Vero IPV draft 2 03/7/2002. RIVM Archive, file no. 1059290.

143 Most airlines have stopped transporting nonhuman primates for research purposes after protests from activists. Meredith Wadman, 'Activists Ground Primate Flights', Nature News, 483.7390 (2012), 381 <https://doi.org/10.1038/483381a>.

144 Bijlage DO Vero IPV draft 2 03/7/2002. RIVM Archive, file no. 1059290.

145 Email van H. Kreeftenberg aan P. Everts: gecorrigeerd verslag RVP planningsoverleg 17/10/2002. Verstuurd op 04/11/2002. RIVM Archive, file no. 1059292.

146 Interview R4; Sheets, History and Characterization.

147 Controle virusvaccins; aanvraag voor serologische screening monkeys, 13/12/2005. RIVM Archive, file no. 1061816.

148 Experiments with Primates NVI 2006-2010, concept 28/04/2006. RIVM Archive, file no. 1215.

'Experiments with Primates NVI 2006-2010', the subject of societal perspectives on the use of nonhuman primates was brought up:

> Of course, all experiments in this area will be conducted in accordance with regulations. Despite this, it is desirable to consider beforehand the societal responses that such animal experiments can elicit and what the answer of the NVI (and indirectly the RIVM and VWS) will be in case societal unrest were to arise. In that case, it is important that the public health benefits of the experiments can be presented clearly.[149]

The document further lists eight categories of experiments that they planned to undertake in the coming years, mostly related to vaccine development, safety, and potency testing of vaccines and other medications. The majority of the experiments they were planning were in collaboration with or commissioned by other institutes.

At that point the RIVM was still co-administrator of the animal facility, and the building where the monkeys were housed was sublet to NVI. Because of this, the RIVM also had a say in the matter. A meeting was held within the RIVM to discuss the matter of continued experimentation on nonhuman primates. According to the meeting's minutes, the RIVM was not *a priori* against research with nonhuman primates, provided that it was in the great and immediate interest of public health and that there were no other options available. To the RIVM it seemed, however, that NVI wanted to take the path of contract research for third parties and conduct experiments with NHPs where there was no acute or great risk to public health.[150] In addition, they saw the plans as 'high risk' when it came to reputation damage and safety of the RIVM and its staff:

> The RIVM has a good reputation regarding (the reduction of) animal experiments, which was previously called de-animalization. The execution of the plans described above [by NVI] is decidedly contrary to this RIVM policy. This may lead to severe reputation damage and the DG of the RIVM does not want to take on that responsibility as license holder (for the law on environmental control) and as having final responsibility for the physical security.[151]

Regarding physical safety, there was concern that staff would be approached aggressively by activists, not only on site but also in their private homes.[152] Finally, the RIVM also expressed disappointment about the communication between NVI and RIVM on this matter. The archival material unfortunately does not show how the discussion between RIVM and NVI continued, but the yearly report on nonhuman animal use showed an increase for 2006 in contract research with primates for NVI, but a reduction in 2007. Based on interviews it is clear that primate research ended soon after.[153]

149 Ibidem.

150 Vergaderverslag 'Proefdiergebruik niet-humane primaten' 8/05/2006. RIVM Archive, file no. 1215.

151 Ibidem.

152 Gespreksnotitie TBV overleg van directies NVI en RIVM op woensdag 17 mei inzake aspecten verbonden aan voorgenomen BSL-3+ en DM-III proefdierexperimenteel werk met non-humane primaten. 13/0506. RIVM Archive, file no. 1215.

153 Interviews R1 & R2.

Although monkeys are no longer used for the production of the polio vaccine in the Netherlands, other nonhuman animals are. Rats are still used for potency testing, albeit less often than in earlier years.[154] Rat use is expected to be reduced further in the near future by applying a 'consistency approach' combined with in vitro tests that are already in use, such as ELISA D-antigen tests.[155] Calves are also still part of the IPV-production process, but non-animal alternatives for fetal calf serum are being sought.[156] In addition to tests for IPV, the Animal Research Center also performs a neurovirulence test in transgenic mice for OPV as contract research for BBio.[157] The WHO approved this mouse test as an alternative to the monkey neurovirulence test in 2003, but at the same time confirmed that a monkey test remained the 'golden standard' and should be used for new seed lots or when changes in the manufacturing process are made.[158]

Recently, more countries (such as the US) have switched back to IPV. This is considered crucial for the eventual complete eradication of polio, since OPV has the disadvantage of causing polio in one in five million vaccinated people (since it is a live rather than inactivated virus

3.8 CONCLUSION

We have seen that the lives of different generations of RIVM monkeys were radically different from one another due to a wide variety of developments both within the RIVM and in science and society in general. First, we saw how in the 1950s and 1960s, long-tailed macaques living in the wild in Southeast Asian were caught in large numbers and flown to the Netherlands where they were killed shortly after arrival (if they survived transport) so that their kidneys could be used for polio vaccine production. Although nonhuman animal testing was a generally accepted and growing business during this period, RIVM researchers had pressing reasons to reduce monkey use as soon as possible: macaques were increasingly difficult to obtain, expensive, and often 'unclean' or of 'poor quality'. Driven by this 'monkey problem', the IPV production process was adapted by implementing technoscientific improvements such as the use of microcarriers, kidney perfusion, and cell subcultivation. This resulted in an increased yield per 'gram of monkey' and drastically reduced the number of macaques needed. Ethical motives for reducing monkey use were not found, which is not all that strange considering that the reduction in monkey use took place before the Animal Testing Act was implemented and before "reduction" became an explicit policy focus as part of the 3Rs discourse that became popular from the 1980s onwards.

In the 1980s, we saw the effects of the Animal Testing Act and 3Rs policy, and "ethics" became part of the discourse. The attention for macaque wellbeing increased, both as part of optimizing monkey supply and, importantly, also as a goal in and of itself.

154 A. Gomersbach (personal communication, 25/02/2021).

155 Coenraad Hendriksen and others, 'The Consistency Approach for the Quality Control of Vaccines', Biologicals, 36.1 (2008), 73–77 <https://doi.org/10.1016/j.biologicals.2007.05.002>.

156 'Fetal Calf Serum Free Database' <https://fcs-free.org/> [accessed 24 February 2021].

157 A. Gomersbach (personal communication, 25/02/2021).

158 Eugenia Dragunsky and others, 'Transgenic Mice as an Alternative to Monkeys for Neurovirulence Testing of Live Oral Poliovirus Vaccine: Validation by a WHO Collaborative Study', Bulletin of the World Health Organization, 81 (2003), 251–60 <https://doi.org/10.1590/S0042-96862003000400006>, 259

Refinement measures gave macaques more space to move and interact with each other and a more diverse material environment (e.g., toys), as well as opportunities to form more complex social relations when in group housing. These measures often also served human interests, who benefitted when tested animals were healthy and reproduction rates were high. In situations of conflicts of interest however, animal welfare was second to human safety or economic interests.

The breeding program also led to an increased focus on macaque welfare as it dramatically altered the day-to-day practices in the polio laboratory and interactions between primates (human and nonhuman). To successfully create new lives, humans had to become attuned to the rhythms of macaques and their psychological needs, leading to much more intimate contact. Objectification of individual monkeys became more difficult and more opportunities for micro-challenges to a human/animal dichotomy arose. Relations emerged in which monkeys and humans materialized as objects and researchers, but sometimes also as babies, parents, caretakers, threats, play buddies, et cetera. Yet, in the end, all monkeys returned to the status of object when they were "sacrificed".

The Animal Testing Act and 3Rs discourse entailed not only increased concern for nonhuman animal welfare, but also a favoring of primates over other species such as rodents. Non-human primates moved up the species hierarchy and replacing them with 'lower' animals became seen as more ethical. Although nonhuman primates have seen their 'status' (in the eyes of humans) increase over the past decades, they remain property in a legal sense. In general, one can say that the ethically motivated changes made in law and policy regarding nonhuman animal experimentation have been more about welfare than about rights or a fundamental rethinking of the ethical position of nonhuman animals vis-à-vis humans. Law and policy continue to reproduce a human/animal dichotomy, whilst creating a stronger hierarchy within the 'animal' category. Concern for nonhuman primates' suffering has continued to increase, however, and the threshold for human benefit justifying their use has risen accordingly. Yet nonhuman primates can still be experimented on when humans feel this is absolutely necessary, and humans remain the only species with rights. In other words, Nozick's 'Utilitarianism for animals, Kantianism for people' still holds.[159] Taking a different ethical position, animal activists have protested against the use of monkeys both by RIVM and internationally and pressured airlines to end the transport of primates for testing purposes. These activists were not successful in convincing policy makers that primate use should never be allowed, regardless of human needs. Still, the subsequent unwillingness of airlines to transport monkeys did pose an additional barrier to the RIVM when it came to continuing the use of macaques in the 21st century.

Despite nonhuman primate use becoming more controversial, the presence of an in vitro alternative since 1982 (the Vero cell line), pressure from activists and the AEC, and the economic advantages of this alternative, it took until 2005 for macaques to be replaced by these Vero cells. Strong risk aversion and a lack of a sense of urgency worked together to keep this from happening. Because only a few monkeys were used each year, there was no immediate need to change the production process. In other

159 Robert. Nozick, Anarchy, State, and Utopia (New York: Basic Books, 1974), 39. Although the use of great apes for research has been banned in the EU, there remains the option to overturn this decision in a situation of great human need. In addition, great apes do not possess the right to not be experimented on without consent (in contrast to humans), rather humans are prohibited from experimenting on great apes.

words, the successes achieved in reducing the numbers of monkeys in the end held back a complete replacement of monkeys. A sense of urgency only emerged when a new shortage of monkeys was looming as a result of polyoma infections and increased monkey use for IPV-export. By this time, Vero-IPV was widely accepted and no longer considered a risk. In fact, MK-IPV had become an economic risk. It could therefore no longer be claimed that the macaques were *needed,* which ultimately delegitimized their use.

CHAPTER FOUR

E is for Ethics? The Formation of Animal Experiments Committees in the Netherlands and at the RIVM in particular

CHAPTER 4: E IS FOR ETHICS? THE FORMATION OF ANIMAL EXPERIMENTS COMMITTEES IN THE NETHERLANDS AND AT THE RIVM IN PARTICULAR

4.1 INTRODUCTION

'It is harder to get permission to perform an experiment on animals than it is on people!' is a statement I have heard many times during the course of this research. The statement is usually uttered semi-jokingly to indicate how well-regulated nonhuman animal experimentation is and how carefully the decision to experiment on nonhuman animals is made. While the existence of these regulations is sometimes seen as a bit of a nuisance, a legally required ethical review of nonhuman animal experiments is generally accepted by scientists and considered to be part of doing 'good science'. As discussed in Chapter 2, I adopt the term 'good science' following Druglitrø, who has shown how the use of nonhuman animal experimentation in Norway was constructed as a 'good science' by developing a 'scientific mode of care' (including regulations) in which nonhuman animal and human welfare were constructed as interdependent.[1]

In this chapter, I analyze how a legally required ethical review by Animal Experiments Committees (AECs) came to be considered 'good science' in the Netherlands. In 1987, the Dutch government announced that AECs, and therefore some sort of 'ethical test' of nonhuman animal experiments, would become part of national legislation. This was cause for concern among scientists, who worried that regulations would hinder scientific progress. They also worried about the risks involved if regulations required more openness about nonhuman animal testing practices. To influence this legislation, they organized themselves and made proposals for the law on AECs. Rather than rejecting AECs altogether, they embraced them but tried to convince the government to organize the committees in such a way that all decision making was done internally by scientists.[2] Animal advocacy organizations meanwhile also joined forces to influence the legislation by commissioning an advisory report proposing far-reaching regulations, such as making AEC reviews legally binding and the inclusion of an ethicist in each AEC. In other words, different stakeholders proposed different versions of ethical reviews and of the meaning of 'good science' in the context of nonhuman animal experimentation. To understand how AEC legislation came about and has changed over time, I analyze the positions of the different stakeholders as well as the discursive strategies they used to influence the debate. I first discuss how AECs and AEC legislation came about in the Netherlands (4.2). This is followed by an analysis of national discussions about AECs after their regulation in 1997 (4.3). I then move from the national to the institutional level to take a closer look at the creation of the AEC-RIVM, including a discussion of how they dealt with the issues of how to perform an ethical review and how to measure suffering (4.4). In section 4.5, I detail how the AEC-RIVM fared after its formal recognition in 1997 and include a discussion of three specific cases that were reviewed by the

1 Tone Druglitrø, '"Skilled Care" and the Making of Good Science', Science, Technology, & Human Values, 43.4 (2018), 649–70 <https://doi.org/10.1177/0162243916688093>.

2 The debates around AECs show many similarities to the debates around Medical Ethical Review Committees (METCs) in the Netherlands, see: Noortje Jacobs, 'Ethics by Committee: Governing Human Experimentation in the Netherlands, 1945-2000', 2018. <https://doi.org/10.26481/dis.20180620jn>.

AEC-RIVM. Finally, some conclusions are presented in section 4.6.

Before continuing, I would like to come back to the opening quote, to explain why this subject is important in a research project that aims to 'decenter the human' and bring nonhuman animals to center stage. Even though this chapter is mostly about humans, I argue that it is crucial in understanding the lived experiences of nonhuman animals featured in other chapters. In considering the opening quote, it is good to be aware of what AEC permission means for individual nonhuman animals. In the case of humans, recognition of their intrinsic value has led to the creation of inviolable human rights that protect them, at least on paper, from non-consensual experiments and experiments that are likely to cause severe suffering and death. For members of other species, this has not been the case and an AEC decision affects every aspect of a tested animal's life from conception to death. Consequently, analyzing the creation and functioning of regulations and AECs is of great importance for understanding and accounting for the lived experiences of nonhuman animals in experimental settings. Therefore, in the conclusion I also reflect on what AECs' inclusion in understandings of 'good science' has meant for individual tested animals.

4.2 THE CREATION AND LEGISLATION OF AECS IN THE NETHERLANDS

> In a decision regarding animal testing, it is in fact about weighing the necessity of the experiment against the suffering that can be inflicted upon the animals. In the past year, the conviction has emerged that a it is not enough if such a judgement is made by only the one performing the animal experiments. With this, the first reason for proposing amending the Animal Testing Act is given, that is giving legal basis to Animal Experiments Committees. By these we mean committees that have the task to review the ethical permissibility of specific animal experiments based on certain norms of weighing and criteria of execution. [3]

This is how State Secretary of Welfare, Public Health, and Culture H.J. Simons explained the inclusion of AECs in the amended Animal Testing Act of 1992. From then on, AECs would be part of national legislation. In the explanatory memorandum, he described the process leading up to the final legislation.

The first Dutch reference to AECs can be found in the report 'Animal Testing at Institutes of Higher Education', written in 1978 by the Minister of Education and Science. In the report, he suggested creating advisory committees concerned with various aspects of animal experimentation. This idea was developed further in the 1982 report 'Ethics and Legislation' written by the Dutch Association of Laboratory Animal Science (NVP). They recommended the creation of Animal Experiments Committees which would advise license holders on all matters regarding nonhuman animal experimentation, including the permissibility of experiments. The government committee for advice on animal testing CvAvdD agreed with this advice and largely adopted it in their 1985 report

3 H.J. Simons, Memorie van Toelichting Wijziging Wet op de Dierproeven, Den Haag, 1992. Retrieved May 13 2020 from https://www.parlementairemonitor.nl/9353000/1/j4nvgs5kjg27kof_j9vvij5epmj1ey0/vk11nlgu9cy5/f=/kst22485n3k2.

'Ethical Principles and Animal Experimentation'.[4] This report advised against national legislation and in favor of leaving ethical reviews up to AECs. According to AEC-RIVM member B.C. Kruijt, there was general agreement in the Netherlands that national regulations should wait until there was more experience with AECs. This was in part based on the experiences in Sweden, where regulations had been created in 1979 which already needed to be modified a few years later.[5]

The State Secretary of Welfare, Public Health, and Culture asked the Dutch Association for License Holders in Animal Testing (NVVD) to comment on the advice. In response, the NVVD organized a survey among license holders which showed that in 1986 about 90% of animal experiments were performed at institutions where an AEC was present or being created. This revealed a sharp increase since 1980, when only 17% of institutions had an AEC.[6] It is important to note here that this does not mean that 90% of the experiments were reviewed by AECs, nor does it mean that 90% of institutions had an AEC. The practices of the AECs varied considerably and not all experiments were reviewed. The percentage is so high because larger institutions that perform most of the nonhuman animal experiments were likely to have an AEC. A survey by Vorstenbosch and Stafleu showed that fourteen out of eighteen universities had an AEC in 1988, whereas only seven out of twenty businesses had one. In their report 'AECs in the Netherlands: Facts, Problems, and Perspectives', they also found that AECs only gave non-binding advice to license holders and that the aspects considered in reviews varied between (types of) institutes.[7] Many AECs conducted three types of reviews: scientific, ethical, and Laboratory Animal Sciences. In universities, however, the scientific review was often done by a separate committee and in businesses economic aspects were considered as well.

Despite many institutes following the suggestions first made by the NVP and later by the State Secretary to create an AEC, on March 10, 1987, in response to ongoing parliamentary demand, State Secretary Dees promised the Dutch Parliament that he would create legislation to make AECs mandatory.[8] Scientists were unpleasantly surprised by this move and concerned about the consequences for their work. They became genuinely alarmed when the report 'Reviewing Animal Experiments' was published in August 1987. This report was written by F.C.B. van Wijmen en Ariane den Uyl of the research group Health Law at the University of Limburg but was commissioned by an alliance of two animal protection organizations (NBBV and NVBD). The report caused alarm due to its content along with a statement (reportedly) made by State Secretary Dees that he would take the report as guidance.[9] Scientists responded by forming an ad hoc committee within the Royal Dutch Academy of Arts and Sciences (KNAW) which drafted its own advice and attempted to convince politicians of the catastrophic consequences the proposals of the 'Reviewing Animal Experiments' report would have.

4 Commissie van Advies voor de Dierproeven, Advies 2. Ethische beginselen en dierproeven. Leidschendam, Ministerie van Welzijn, Volksgezondheid en Cultuur, 1985.

5 B.C. Kruijt, Dierexperimenten-commissies, Berichten uit het RIVM 1987, (1988), p. 254.

6 Simons, Memorie van Toelichting.

7 J.M.G. Vorstenbosch & F.R. Stafleu, Dierexperimentencommissies in nederland, Feiten, problemen en perspectieven, 1990.

8 Handelingen Tweede Kamer 1986-1987 (10/03/1987) 2991; Kruijt, Dierexperimenten-commissies.

9 Diskussienota ten behoeve van de adhoc komissie dierproeven van de KNAW, February 1988, 1 RIVM Archive, file no. 5179.

In 1988, all parties were invited to a hearing on the matter, after which the CvAvdD advised the state secretary on how AECs should be legislated.

4.2.1 The Report

Animal advocacy organizations *NVBD and NBBV* asked researchers Van Wijmen and Den Uyl to write a report advising the government on legislation concerning the ethical review of animal experiments by AECs. The two researchers based their findings on a survey of people working in nonhuman animal experimentation and presented their recommendations to State Secretary Dees on December 15, 1987.[10] These recommendations, if followed, would entail a drastic change from the way AECs had operated so far. They advised that all experiments should be ethically reviewed by an AEC; a central AEC should be created where license holders could object if they disagreed with the AEC; and their composition requirements should be enacted which included requirements of an independent expert (ethicist or legal scholar). The NBBV and NBVD recommended legislation that went even further: all AEC advise should be legally binding and made public.[11] They further stated, responding to the 'Ethical Principles and Animal Testing' report, that the government could and should provide more guidelines for the ethical review process. What is interesting here is the strategies used by activist organizations, who tried to influence regulations by recruiting (legal) scientists who could in turn influence politicians and policy makers. Also interesting is that they were taken seriously by politicians as stakeholders and seen as knowledgeable (even though, as we will see next, there were efforts by KNAW committee members to disqualify their work as 'too emotional'). This shows that although the 1980s and 1990s are often characterized as a period with fierce animal activism, including illegal actions, animal advocacy organization used many different kinds of strategies and in the Netherlands stayed on good terms with politicians (see also Chapter 2).

4.2.2 The Response

Scientists working in animal testing worried that the government would implement the advice given in the report and responded by forming the Ad Hoc Committee of Animal Testing in the KNAW (the Dutch National Academy of Arts and Sciences).[12] The former DG of the RIVM Hans Cohen was the chair of this committee.[13] A discussion note was circulated to committee members in February 1988 stating that the aim of the committee was to write a report consisting of two parts: a response to the report by Van Wijmen en Den Uyl and their own position regarding AEC legislation. The note was

10 Eerste Kamer Stukken 1987-1988, nr. 190a (26/05/1988), Beleidsdebat over onderwerpen rakende het Ministerie van Welzijn, Volksgezondheid en Cultuur; Memorie van Antwoord, 40. https://repository.overheid.nl/frbr/sgd/19871988/0000098304/1/pdf/SGD_19871988_0000527.pdf

11 Kruijt, Dierexperimenten-commissies, 254.

12 Diskussienota ten behoeve van de adhoc komissie dierproeven van de KNAW, February 1988. RIVM Archive, file no. 5179.

13 Other members were: J.H. Bergsma of TNO, J. Joose of Zoological Laboratory of VUA, F.L. Meijler of the Interuniversitair Cardiologisch Instituut Nederland (KNAW), V.M. Wiegant of the R. Magnus Instituut RUU, LF.M. van Zutphen of Proefdierkunde RUU, C.W. Pool of the Nederlands Instituut voor Hersenonderzoek (KNAW). Appendix 2 Diskussienota ten behoeve van de adhoc komissie dierproeven van de KNAW, february 1988. RIVM Archive, file no. 5179.

discussed during the committee's first meeting on March 3, 1988.[14] Over the course of several meetings the newly formed committee wrote a joint response and position on the matter and sent it to the CvAvdD in June 1988.[15] They communicated that they were, in principle, fine with making an ethical review mandatory in the Animal Testing Act. However, discussions within the committee departed from the starting point that:

> [...] there is a societal need for an ethical review of animal experiments. The committee supports this need and wants to point out that in the desire for regulation that follows from this, a step needs to be taken towards those that are of the opinion that lab animals have to be dealt with very carefully, but that there also needs to be enough space left open for an optimal functioning of animal experimental research.[16]

They felt that the recommendations made by Van Wijmen en Den Uyl did not leave enough space for experimental research and therefore had to be rejected as overregulation.[17] In their response to the report they argued that in the opinion of the KNAW:

> There is currently the potential that emotional arguments are getting too much attention in proposed legislative changes. Especially the promise made by State Secretary of Welfare, Public Health, and Culture, D. Dees, in the UCV[18] of March 10, 1987 that the results of the research conducted by Van Wijmen and Den Uyl at the capacity group Health Law of RU Limburg would be used, fills the KNAW with (great) concern.[19]

The committee further stated that were the proposed legislation to be adopted, it would have '[...] catastrophic consequences for the Dutch research climate'.[20] Reviewing every single experiment, they argued, would pose an enormous financial and administrative burden on research institutes.

Instead, the committee proposed that the law should be approached 'dynamically', with as minimal legislation as possible. This, they argued, would be in line with the Dutch deregulation trends and, more importantly, would prevent research from moving abroad where regulations were less strict. In their proposed version of the law, the AEC advice would be non-binding and could be overruled by the license holder. Additionally, they argued that the composition of AECs should be at the discretion of license holders and that the membership of an ethicist should not be required. Instead, to help with the ethical review process, they suggested that members should take a course in ethics. The

14 Letter from C.M.A.W. Festen to Ad Hoc Committee, 11/3/1988. RIVM Archive, file no. 5174

15 Letter from H.H. Cohen June 1988 RIVM Archive, file no. 5174.

16 Diskussienota ten behoeve van de adhoc komissie dierproeven van de KNAW, February 1988, 2. RIVM Archive, file no. 5179.

17 Document Ad Hoc Commissie KNAW. RIVM Archive, file no. 5179.

18 Uitgebreide Commissievergadering (extended committee meeting, a public meeting with a committee of parliament).

19 KNAW standpunt met betrekking tot het instellen van een wettelijke basis ten behoeve van de ethische toetsing van dierexperimenten, concept, 1988, 1. RIVM Archive, file no. 5179.

20 Ibidem.

KNAW also found it important that the composition of AECs remained confidential.[21] In a letter to the committee, Cohen mentioned further concerns regarding confidentiality and the potential involvement of 'outsiders':

> The confidential aspect of the information that external committee members receive, has to be guaranteed. It has to be prevented that some of the involved outsiders ('buitenwacht'), who (as is clear from newspaper publications) aim for the eradication of all animal research and twist or deny the meaning of animal research for societal achievements, will have direct access to the scientific thinking patterns of the involved working unit. [...] Misuse of information should be prevented by an oath or promise/pledge by committee members and violation thereof should be punishable by law even if just to counterbalance the threat of a prison sentence for researchers.' [22]

Regarding who should decide the permissibility of experiments, the committee thus advocated for all decision-making power to remain internal; government and other outsiders (including professional ethicists) were not to be involved.

Lastly, the committee pointed out important differences between 'basic' research and other research. They argued that an ethical review of basic research is not possible and, according to committee member Bergsma, also not necessary because the outcomes are unpredictable. Pilot studies and studies with completely new techniques should therefore be exempted from AEC reviews.

4.2.3 The Hearing and Compromise

A hearing about AECs was organized on September 28, 1988. The ad hoc committee, represented by Cohen, was invited to give advice and ask questions. Based on all the written and oral input, the CvAvdD then wrote a final report entitled 'Animal Experiments Committees' on AEC legislation, which they presented to the minister. In this report, the CvAvdD described the process leading up to their advice, their legislative recommendations, and the comments made by stakeholders. Based on this report, the Animal Testing Act of 1977 was amended several times and in 1996 a revised Animal Testing Act was accepted. This revised law included legislative changes regarding AECs and additional changes as a consequence of the 1986 EEC directive 86/609/EEC on the protection of animals used for scientific purposes. Regarding AECs, the Dutch Animal Testing Act was amended in several ways over several stages. In 1993, new legal requirements meant no animal experiment was permissible without the direct advice of an ethical committee (AEC). Each license holding institution was not required to create their own AEC, however; using another institution's AEC was permitted as well. The ability to share AECs was preferred from a "deregulation" standpoint and intended to prevent high costs for small institutions. Ethical reviews had to be performed by an AEC approved by the Dutch government.[23] The compositional requirements for AECs were specified in the 1994 amendment to the Animal Testing Act (Art. 18a, part 2):

21 Ibidem.

22 Letter from H.H. Cohen to Ad-hoc committee secretary C.W. Pool (9/2/88), 3. RIVM Archive, file no. 5174.

23 Simons, Memorie van Toelichting.

a. There should be at least seven members, including the chair;
b. The committee should (in equal numbers) be composed of experts in the area of animal experimentation, experts on lab animals and their protection, and experts on ethical reviewing;
c. At least two of the experts should not be involved in animal testing;
d. At least two of the members should not be in a work relationship with the license holder;
e. Other members should, when involved in an animal experiment, not be involved in advice about that experiment.[24]

In the revised Animal Testing Act of 1996, alternatives to animal testing were added as a fourth required area of expertise.[25] The law did not, however, provide any criteria to judge the expertise of members nor specify a specific education or background. The Central Committee on Animal Experimentation (CCD)[26] did create profiles for each of the four areas of expertise that were meant to be used by AECs in finding suitable members. These were not legally binding however and a 2004 study found that they were not well known among AECs.[27]

With respect to the nature of the AEC review, advice, or decision, State Secretary Simons explained that he had opted for a compromise between the legislative suggestions of Van Wijmen en Den Uyl and the ad hoc committee of the KNAW. The AEC review served as advice to the license holder and was not definitive. However, if the AEC advised against an experiment the license holder was required to seek further advice from the CCD before being permitted to perform the experiment. According to Simons, this made the animal testing legislation stricter than the legislation on human experimentation, where the element of a central advisory body was missing. This extra element was needed because: '[...] here there is of course [no possibility that— as is the case in research using human test subjects—the test object forms a judgement about the experiment before submitting themselves to the experiment.' [28]

Overall, the AEC legislation was less "dynamic" than scientists would have hoped, but more so than recommended by animal advocacy organizations. Especially in terms of how ethical reviews were performed, the legislation gave very few guidelines, leaving much of the responsibility up to license holders. In 1984, the state secretary had asked the CvAvdD to research whether it would be possible to come up with general ethical principles that could be used for deciding the permissibility of nonhuman animal experiments and that were acceptable to society in general. The committee wrote the report 'Ethical Principles and Animal Experimentation' in which they spoke of an 'ethics of responsibility', in line with the policy note 'Government and Animal Protection' of 1981.[29] This note stated that: 'The animal protection policy will have to be developed from the

24 Wet op de Dierproeven, amendement 1994, art. 18a part 2.

25 Wet op de Dierproeven, 1996. Retrieved from https://zoek.officielebekendmakingen.nl/stb-1996-500.html.

26 The CvAvdD changed its name to Central Committee Animal Experiments (CCD).

27 Freriks, and others, Noodzakelijk Kwaad; Evaluatie Wet op de Dierproeven, 2005, 56 (referring to an internal report by Sandra Swart: Dierexperimentencommissies: deskundig oordeel over dierproeven, Utrecht, Nationaal Centrum Alternatieven voor Dierproeven, november 2004).

28 Simons, Memorie van Toelichting.

29 Commissie voor Advies voor de Dierproeven, Ethische Beginselen en Dierproeven, Leidschendam, 1985.

recognition of the intrinsic value of the individual animal. The policy should be aimed at protecting the animal as much as possible against human acts that harm their physical and ethological wellbeing'.[30] While using and killing other animals in experimental and other settings would seem in contradiction with this, the statement was translated into practice to mean that people should account for harming nonhuman animals. Overall, the CvAvdD committee concluded that ethical principles could be formulated only very generally and that they would have to be operationalized within AECs.

The revised law of 1996 added two articles relevant to ethical reviews. Article 1b stated that the intrinsic value of the animal should be taken as the general starting point in the execution of this law. Article 10b stated that performing an animal experiment that causes severe suffering was to be disallowed if the experiment was not in the interest of essential needs of humans or other animals (thus implying that experiments on nonhuman animals in the interest of non-essential needs are allowed when they cause mild or moderate suffering). The recognition of intrinsic value is generally seen as incompatible with the utilitarian approach implied by the (one-directional) weighing of suffering and benefits that the law requires. It is not surprising then that the ethical review continued to be subject of debate in the following decades.

4.3 AECS AFTER 1997: CONTINUED DISCUSSION

National discussions after 1997 were not new but rather continuations of unresolved discussions during the creation of the AEC legislation, namely the issue of the ethical review— how to perform it, its relationship to the 3Rs, and issues of openness and outsider involvement.

In 2005, a report entitled 'Necessary Evil' (*Noodzakelijk Kwaad)* by Freriks et al. was published which evaluated the Animal Testing Act.[31] The report included an extensive evaluation of the performance of AECs and made strong statements about the (lack of) ethical reviewing. Further, it put forward recommendations for much more openness and involvement of the public, including animal advocacy organizations. Freriks et al. noticed that experiments were rarely rejected and while they agreed that AECs likely had a preventive effect (see section 4.5), they found the overall situation unsatisfactory in terms of the credibility of the law and how AECs were functioning—a sentiment also expressed by activist organizations.[32] The authors stated that: 'Also in relation to lab animals, the adage "justice must not only be done, it must also be seen to be done" holds.'[33] Based on interviews with AEC members, public statements made by (former) AEC members, and scientific literature on the matter, the authors found indications that the 3Rs overshadowed actual ethical judgements in AECs. The study 'Ethics in Animal Experiments Committees' by Schurgers, based on 26 interviews with AEC members,

30 Ministerie van Cultuur, Recreatie en Maatschappelijk Werk, Rijksoverheid en Dierenbescherming., 1981, 3.

31 A.A. Freriks and others, *Noodzakelijk kwaad: Evaluatie van de Wet op dierproeven*. (Evaluatie regelgeving; No. 18) (ZonMw, 2005) <https://edepot.wur.nl/35442>,.

32 Regarding this 'prediscussion', they also note that while this may be efficient, it could possibly also be a threat to independence. Therefore, they recommended that in most cases AECs should not have spoken with the researchers prior to judging the proposal. Freriks et al., Noodzakelijk kwaad, 60.

33 Ibidem, 61.

found that animal ethical concepts such as intrinsic value hardly played a role in ethical reviews. The concepts seldom came up and there was no consensus about their meaning.[34] Schurgers also concluded that the AECs did not really perform an ethical weighing of benefits against suffering, but rather verified whether the benefits being claimed were indeed present and whether the 3Rs were applied sufficiently. More recent research by Poort et al. (2013) and McLeod & Hartley (2018) also showed that the ethical review process mostly focused on technicalities and the 3Rs rather than on broader political questions such as the moral status of nonhuman animals.[35] Noortje Jacobs found a similar situation in her analysis of Dutch Medical Ethical Review Committees (METCs), which reviewed experiments on humans. She argues that these committees function as 'epistemic filters' that weed out bad quality research by reviewing procedures, methods, and scientific quality, rather than contemplating ethical issues relating to, for example, patient rights and humanity.[36] In this process 'scientifically good' (and in the case of nonhuman animal testing also 'compliant with the 3Rs') becomes equated with 'ethically good'.

Freriks et al. (2005) concluded that the ethical review process needed to be lifted to a higher level. However, respondents pointed out a number of difficulties. The report cited one respondent saying that: 'That whole image of a scale, in which lab animal suffering should be weighed against societal or scientific benefit of the experiment, is not right in my eyes. You are comparing apples and oranges.'[37] The difficulties surrounding the ethical review were also explored in the three-part book series *AECs in Discussion* (*DECs in discussie),* published between 2004 and 2009.[38] Some authors, such as Jac. Swart and Ronald Tramper, argued for pragmatism: eclectically combining different ethical perspectives however was deemed necessary. Others, such as Mieke Boon, argued that the ethical tensions this eclectic combining results in cannot be ignored.[39] In

34 R. G. Schurgers, 'Ethiek in dierexperimentencommissies: het belang van een dierproef gewogen tegen het ongerief voor de proefdieren' (Kennispunt Bètawetenschappen, Universiteit Utrecht, 2005), pp. 1–89, 49.

35 Lonneke Poort, Tora Holmberg, and Malin Ideland, 'Bringing in the Controversy: Re-Politicizing the de-Politicized Strategy of Ethics Committees', Life Sciences, Society and Policy, 9.1 (2013), 11 <https://doi.org/10.1186/2195-7819-9-11>; Carmen McLeod and Sarah Hartley, 'Responsibility and Laboratory Animal Research Governance', Science, Technology, & Human Values, 43.4 (2018), 723–41 <https://doi.org/10.1177/0162243917727866>.

36 Jacobs, Ethics by Committee, 233.

37 Quote of a former AEC chair in Freriks et al., Noodzakelijk Kwaad, 60.

38 DEC's in discussie: de beoordeling van dierproeven in Nederland, ed. by Jacobus Adrianus Antonius Swart, Jan Wolters, and Hubertus Andreas Everhardus Zwart, Reeks dierproeven, dl. 1 (Budel: DAMON, 2004); Kan het ook anders? Beschouwingen over alternatieven voor dierproeven, ed. by Jacobus Adrianus Antonius Swart, Geny Groothuis, Jean Horbach and Jan van der Valk, Reeks dierproeven, dl. 2 (Budel: DAMON, 2006); De Weging Gewogen, Beschouwingen over ethiek en dierproeven, Reeks dierproeven, dl. 3 (Budel: DAMON, 2009). In part one of this book series, many different authors responded to the question: to what extent can an AEC make a weighing between moral costs and benefits of an animal experiment that is supported by society, in the context of conflicting interests and ideologies (page 8)? Part two discusses possible alternatives to animal experimentation and part three zooms in on the ethical weighing by AECs.

39 Mieke Boon and others, 'Morele Grenzen van Dierexperimenten Commisies (DEC's)' in DEC's in discussie: de beoordeling van dierproeven in Nederland, ed. by Jacobus Adrianus Antonius Swart, Jan Wolters, and Hubertus Andreas Everhardus Zwart, Reeks dierproeven, dl. 1 (Budel: DAMON, 2004), pp. 79–89.; Jacobus Swart and Ronald Tramper, 'Ethische benaderingen in de afweging van dierproeven', De weging gewogen. Beschouwingen over ethiek en dierproeven, 2009, 19–28.

part three of *AECs in Discussion*, Bert Musschenga argued that the "intrinsic value of an animal" is a useless concept and Vincent Pompe even questioned whether suffering of nonhuman animals should be considered.[40] Not only is weighing itself described as difficult, because of the incommensurability of the things being weighed, so is measuring the suffering and benefits.[41] Some ethicists have attempted to make quantitative frameworks, such as the Utrecht-model developed by Stafleu et al., where points are awarded for certain benefits.[42] But these attempts have been met with skepticism from AEC members and also turned out not to work very well in practice, according to a study done by Schurgers.[43] He tested out the quantitative model which Stafleu et al. developed by giving seven AECs the same cases to judge. He found 'anticipatory valuing' and also found that AECs would increase assigned numbers to prevent rejecting an experiment. In 2005, Freriks et al. came to the general conclusion that:

> Most AEC-members simply seem to be unwilling to reject a protocol that is methodologically and lab animal scientifically sound, just because the benefit of the experiment would not outweigh the suffering caused. […] On top of that, many AEC-members will honestly be of the opinion that human interest, how seemingly small it may be, in the end prevails over animal interest, as long as a serious attempt has been made to minimize lab animal suffering as much as possible.[44]

In 2016, the Dutch government wrote the 'Ethical Review Framework for the Use of Lab Animals. Practical Guidelines for AECs'.[45] Although the document was meant to be a guideline, the authors stated that: 'No guidelines can be given for how to weigh the interests and the related values of various stakeholders against each other'.[46] Instead, the framework described ethical perspectives (consequentialism, deontology, and virtue ethics), stakeholders (target group of the project, lab animals, license holder/researchers, target animal, others with interest such as society at large), and values (wellbeing, autonomy, justice). The authors asked AECs to not only consider consequences when weighing experiments, but also the other two ethical perspectives, thus proposing an eclectic approach. The document did not mention how to deal with the incompatibility of these

40 Bert Musschenga, De rol van het begrip 'intrinsieke waarde' in de dierethiek in De Weging Gewogen, Beschouwingen over ethiek en dierproeven, Reeks dierproeven, dl. 3 (Budel: DAMON, 2009), 38-47; Vincent Pompe, Dierenbewustzijn: erkennen zonder kennen in De Weging Gewogen, Beschouwingen over ethiek en dierproeven, Reeks dierproeven, dl. 3 (Budel: DAMON, 2009), 48-57.

41 Ger ter Horst, Is ongerief objectiveerbaar? In De Weging Gewogen, Beschouwingen over ethiek en dierproeven, Reeks dierproeven, dl. 3 (Budel: DAMON, 2009), 58-67; Jac. Swart, De afweging van belangen in dierproeven in De Weging Gewogen, Beschouwingen over ethiek en dierproeven, Reeks dierproeven, dl. 3 (Budel: DAMON, 2009), 68-78.

42 Stafleu and others, Ethiek, dierproeven en de afweging van menselijke tegen dierlijke belangen. Centrum voor Bio-ethiek en gezondheidsrecht, Utrecht, 1997.

43 Schurgers, Ethiek in dierexperimentencommissies, 44.

44 Freriks et al., Noodzakelijk Kwaad, 68.

45 Cenrale Commissie Dierproeven, Ethisch toetsingskader voor proefdiergebruik: Praktische handreiking voor Dierexperimentencommissies, 2019. Retrieved from https://www.centralecommissiedierproeven.nl/documenten/formulieren/16/6/6/ethisch-toetsingskader.

46 Ibidem, 6.

different ethical perspectives that had been pointed out by other authors such as Boon.

The guideline also stated that social and cultural perspectives should be taken into account together with ethical perspectives:

> In current society, it does not go without saying anymore that every aim that benefits humans outweighs the interests of the animal. Research shows that humans (70%) have a strong emotional bond with animals and that they find animal welfare very important (de Cock Buning, 2012). Society does award different species a different status. This can be seen for example in the European Guideline in which, by setting stricter conditions for the use of nonhuman primates, dogs and cats, a different status is also assigned to different species of lab animals (Guideline 2010/63/EU, Art. 31). This means that the interests of different species can be weighed differently.[47]

Although not mentioned in the guidelines, this statement shows that an anthropocentric ethical perspective was also included in the ethical framework (in addition, of course, to the anthropocentrism reflected in the one-directionality of the ethical weighing the law prescribed). AECs were asked to consider human preferences and feelings for certain nonhuman species in deciding the permissibility of experiments. In other words, using a nonhuman animal for an experiment of a species that humans do not like was preferred over using a nonhuman animal of a species that humans do like, not because the first suffers less but because the human suffers less when an unliked animal is used.

Overall, it can safely be concluded that the discussion around how to perform the ethical review was not resolved by creating more guidelines. Freriks et al. also did not see more guidelines as helpful in resolving this discussion. Instead, they recommended procedural changes and changing the type of legal entity that AECs are to that of a governing body, which would require them to be more open as well as to thoroughly substantiate the decisions they make, including on an ethical level.[48] Additionally, they recommended finding a way of involving animal advocates in the procedure.

The recommendation of more openness was met with a great deal of criticism from researchers and AEC members.[49] They were concerned that more openness could delay the procedures and were also worried about what those opposed to animal testing would do with the information.[50] If AECs became a governing body instead of an advisory body their decisions could be requested under the Freedom of Information Act (FOIA, *Wob* in Dutch). In 2000, the Council of State (*Raad van State)* ruled that the AEC was not a governing body, and therefore an FOIA request made by Proefdiervrij to get access to AEC advice was denied.[51] In 2007, however, a different ruling was made when the Party for the Animals made an FOIA request to see advice from the AEC of Wageningen University. The university denied this request, but the court ruled that

47 Ibidem, 6.

48 Freriks et al., Noodzakelijk Kwaad, 73

49 Interview Van Iersel, who participated in the evaluation; Jaarverslag NCA, 2007. RIVM Archive, file no. 1215

50 Ibidem; Freriks et al., p.77

51 KWA, Zo Doende 2000, Den Haag 2001, 14

AEC advice are a 'matter of governance' (*bestuurlijke aangelegenheid*) and therefore are covered by the FOIA.[52] In 2014, the Animal Testing Act was amended again to be in line with the EU-directive of 2010. AECs now gave advice to the CCD, which granted or denied permission for experiments. The CCD is a governing body and therefore CCD advice is covered by the FOIA. The new EU directive also stipulated that a non-technical summary be made available to the public for each project that is approved. Despite this move towards more openness, authors such as Poort et al. still questioned whether the 'bridge function' of AECs between society and animal experimentation was being fulfilled adequately. Public, and especially dissenting, voices were often excluded from the decision-making process.[53] Based on this critique, Poort et al. argued for a repoliticizing ethical reviews, and including pluralistic viewpoints instead of focusing on achieving consensus.[54] While animal protection organizations were heard by politicians in the process of designing legislation, both these organizations and the public at large had thus far been kept outside of the decision-making process regarding specific research projects and could only find information about animal experiments retrospectively through a FOIA procedure.

We now turn our attention to the AEC-RIVM to see how these national developments played out on the institutional level.

4.4 THE CREATION OF THE AEC-RIVM

During the late 1970s, the Working Group Lab Animals changed into the Lab Animal Committee of the RIVM, which consisted of representatives of each sector involved in animal testing. It concerned itself mostly with the quality control of lab animals.[55] Between 1985 and 1986, the Lab Animal Committee of the RIVM transformed into an AEC over the course of several steps. They added two tasks to their responsibilities: reviewing the ethical permissibility of animal experiments upon the request of research groups and advising the board on general policy lines regarding animal experimentation. They also expanded the committee with an external expert in ethics.[56] They saw no reason to include Animal Technicians (ATs) when this was initially discussed in 1985, but this changed quickly and by 1987 ATs had joined the committee.[57] The transition was completed with a name change: first from Lab Animal Committee to Animal Testing Committee and then, one year later, to Animal Experiments Committee.[58]

What the committee explicitly did not want was to become a committee that only concerned itself with ethical questions; the joint treatment of ethical, scientific, and biotechnical aspects in one forum was seen as necessary for forming good judgements.[59] In 1986, when Director General Hans Cohen requested that a separate ethical commit-

52 ECLI:NL:RBAMS:2007:BB2281 Rechtbank Amsterdam, 20/08/2007, AWB 07-2757 WOB and AWB 07-2760 WOB. Retrieved from https://uitspraken.rechtspraak.nl/#zoekverfijn/ljn=BB2281&so=Relevance.

53 Poort et al., Bringing in the Controversy.

54 Ibidem.

55 Verslag vergadering proefdiercommissie 29/12/85 (03/01/86). RIVM Archive, file no. 12092.

56 Letter B.C. Kruijt to J. Ruitenberg, 21/1/86 RIVM Archive, file no. 12092.

57 Kruijt, Dierexperimenten-commissies.

58 Voortzetting vergadering Proefdiercie 28/2/86 RIVM Archive, file no. 12092.

59 Verslag vergadering proefdiercommissie 29/12/85 (3/1/86) RIVM Archive, file no. 12092.

tee be formed, the members of the AEC-RIVM were unanimously opposed.[6061] During a meeting, they asked him to give the current model a chance for at least a year, and they managed to convince him to do so.[62] The conviction that ethical reviews cannot be completely separated from scientific and lab animal science reviews remains firm within the RIVM-AEC until today, despite outside criticism.[63] B.C. Kruijt expressed the AEC-RIVM opinion on the national legislation discussion in an internal RIVM-announcement: 'In our opinion, it is becoming clear that this [AEC] regulation should, according to the majority of stakeholders, be minimalist and that senseless bureaucracy should be avoided in a realistic manner'.[64]

That the responsibilities of the AEC were wider than just the ethical review, can also be seen in the AEC-RIVM 'Rules of Procedure' that were formulated in 1993. Besides ethical review, several other tasks were listed: signaling issues and developments (also on an international level) relating to animal experimentation and advising the DG about these matters; confidential treatment of complaints regarding the use, housing, and treatment of lab animals; formulating criteria for ethically reviewing future animal experiments and evaluating past and running experiments; and supervising responsible use of lab animals and stimulating the use of alternatives.[65]

The legislative changes made to the Animal Testing Act in 1993–1996 required a change of the AEC Rules of Procedure and working method. While the AEC has originally only reviewed certain experiments, the revised law meant that they had to review every experiment. This led to an increase in workload that the AEC could not cope with. In 1996, over 850 experimental designs had to be reviewed, many more than in previous years. This resulted in a backlog.[66] To limit the workload, a system with five categories was devised:

1. Regulatory experiments;
2. Routine, but non-regulatory experiments with little or mild suffering;
3. New, non-regulatory experiments with little or mild suffering;
4. Routine, but non-regulatory experiments with severe suffering;
5. New, non-regulatory experiments with severe suffering.

Experiments in categories three and five had to be discussed in the AEC prior to deciding on the ethical permissibility. For the other categories, a monthly written report was required, and researchers were invited to meet with the AEC once per year and upon request of AEC members (since experiments in categories two and four would

60 It seems likely that Cohen was given the idea by the Swedish example where a review by an Animal Ethics Committee was made mandatory in 1979, the first European country to do so (although committees that are called Ethics Committees generally also consider the 3Rs). Joakim Hagelin, Jann Hau and Hans-Erik Carlsson, 'The Refining Influence of Ethics Committees on Animal Experimentation in Sweden', Laboratory Animals, 37.1 (2003), 10–18 <https://doi.org/10.1258/002367703762226656>.

61 Verslag vergadering dierproevencommissie 19/2/86. RIVM Archive, file no. 12092.

62 Voortzetting vergadering Proefdiercie 28/2/86. RIVM Archive, file no. 12092.

63 Interview Van Iersel, see also 4.5.

64 Kruijt, Dierexperimenten-commissies, 255.

65 Reglement dierexperimentencommissie RIVM 1993. RIVM Archive, file no. 1037871.

66 Jaarverslag 1996 DEC-RIVM. RIVM Archive, file no. 1035575.

have already been discussed in the AEC when they were first conducted).[67] The revised Animal Testing Act also required official recognition of the AEC-RIVM by the Dutch government. This happened on August 11, 1997. How this formally recognized AEC fared is discussed later in this chapter, but first we take a closer look at how the AEC-RIVM dealt with the questions of how to ethically weigh experiments and how to measure suffering.

4.4.1 Ethics?

In addition to debates about AEC legislation and the tasks of the AEC-RIVM, committee members also faced the challenge of figuring out how to put ethical testing into practice. In 1986, the AEC-RIVM decided to expand their committee and invited ethics Professor Robert Heeger to join the AEC, to which he agreed.[68] Heeger was well acquainted with the subject of animal experimentation. In 1979, he gave a lecture entitled 'Norms and Good Reasons' in which he discussed how to decide which norms are relevant for evaluating the permissibility of animal experiments.[69] He explained that he departed from a utilitarian position and that we should consider both instrumental and intrinsic values, the latter of which can be ordered into higher and lower values. As an example, he stated that the health for humans is of higher value than the freedom from suffering for animals. The basis of this statement was not given, but later on he claimed that 'the human has a special place and he is the only being of which moral responsibility can be demanded. But animals and other nature cannot only be seen as resources for the human. They have intrinsic value too'.[70] The intrinsic value of animals is, however, lower than that of humans, due to the capacity of 'social relations between humans such as life, love, friendship, and happiness'.[71] With value-ranking complete, this scale could then be used to evaluate which decision regarding an experiment would lead to the most 'good' overall.

Besides asking ethicist Heeger to join, the AEC-RIVM also turned to reports on ethical reviewing written by other AECs. The RIVM archives contained two such documents: 'Animal Experimental Research at the University of Limburg; Ethical guidelines, rules of procedure of animal experiments' by H.J. Keasberry of the AEC of Limburg University (1992) and 'Limits to animal experimental research; Review procedure' by Theune and De Cock Buning of the Department of Animal Experimental Questions, Faculty of Medicine, Leiden University (1991).[72]

The report 'Animal Experimental Research at the University of Limburg; ethical guidelines, rules of procedure of animal experiments' largely overlapped with Heeger's position in that it centered around instrumental and intrinsic values of nonhuman animals and creating a hierarchy of values. Similarly, the human was positioned as higher than all other animals. Keasberry referred to the utilitarianism of Bentham and Singer as well as to proponents of animal rights, which 'put humans and animals more or less on

67 Bijlage 2 bij Jaarverslag DEC 1996. RIVM Archive, file no. 1035575.

68 Voortzetting vergadering Proefdiercie 28/2/86. RIVM Archive, file no. 12092.

69 A summary of the lecture was published: F. Heeger. Normen en Goede Redenen, Tijdschrift voor Diergeneeskunde, 105 (1980), 147-153

70 Ibidem, 152.

71 Ibidem, 152.

72 Commissies en werkgroepen RIVM: DEC: relgement en vergaderstukken. RIVM Archive, file no. 1037880.

equal footing regarding their treatment'.[73] This position was found unacceptable by the AEC of Limburg University. Instead, they preferred an anthropocentric position, where other animals are 'moral recipients' but only humans deserve moral rights which, according to the authors, are too tied up with human capabilities to extend them to nonhumans.[74] To justify their anthropocentric ethical position, they used the concept of 'moral distance': humans are closer to other humans and they therefore deserve more moral consideration. At one point they argued that moral distance plays a legitimate role in moral judgements, yet at the end of the same paragraph they wrote that moral distance plays a role de facto but that the legitimacy of this role is questionable. Additionally, they mentioned that a non-anthropocentric utilitarian position would mean that experimenting on nonhuman animals would only be acceptable in cases where we would also find it acceptable for certain humans (e.g. comatose humans), which they could not accept. It seems that their ethical position was in part decided in reverse: they could not accept the position of Peter Singer because it would have led to practical consequences they found undesirable.

The report by Theune and de Cock Buning of Leiden University focused more on the steps that could be taken to come to a decision.[75] They developed a step-by-step approach to the ethical review of animal experiments, listing five moments of review: a) formal/legal criteria, b) scientific criteria, c) lab animal science criteria (3Rs), d) ethical criteria, ethical weighing, and e) credibility of researchers. The fourth ethical step was divided further into three parts: 1) making the moral issue explicit, 2) analysis, and 3) weighing. The analysis stage was to consider three ethical principles: do good, do no harm, and respect the intrinsic value of the animal. The principle "do good" considered the benefits of the proposed experiment for: the health of human or nonhuman animal, food production, science, the involved experimental animal (though this occurs rarely). The principle "do no harm" obviously considered the suffering of the nonhuman animal experimented on. The principle "respect the intrinsic value of the animal" had a rather unexpected practical translation into the criterium of 'not performing an experiment causing severe suffering more than once on the same animal'. The report also contained a decision tree for reaching a decision about a specific experiment. This decision tree included not only the parameters 'suffering' and 'benefits', but also 'lab animal science quality' and 'credibility of the researcher'. An experiment causing severe suffering was only approved when the benefit was high, whereas experiments with little to moderate suffering only required moderate benefits for approval. How the recognition of the intrinsic value of nonhuman animals factored into the chart was not made clear.

Overall, the documents show a rather eclectic approach to ethics, including a consideration of utilitarianism, moral duties, responsibility ethics, anthropocentrism, and intrinsic and instrumental values. A utilitarian approach combined with a recognition of the intrinsic value of nonhuman animals causes friction in moral reasoning, which might explain some of the unexpected practical translations of recognizing the intrinsic value of nonhuman animals, as well as the "reverse moral reasoning" in the report by Keasberry. Former chair of the AEC of the VU Mieke Boon wrote in this regard that rec-

73 H.J. Keasberry, 'Animal Experimental Research at the University of Limburg; Ethical guidelines, rules of procedure of animal experiments' (1992), 15. RIVM Archive, file no. 1037880.

74 Ibidem.

75 T. de Cock Buning and E.P. Theune, Grenzen aan dierexperimenteel onderzoek: Toetsingsprocedure, Dierproefvraagstukken, RUL Leiden, 1991.

ognizing the intrinsic value of nonhuman animals is inconsistent with reducing them to an instrument in a one-directional utilitarian weighing, concluding that: 'the practice of AECs is that they operate from an ethical perspective that is incoherent with an ethical perspective in which the intrinsic value of animals is protected'.[76]

AEC-RIVM Secretary Arthur van Iersel recalls that the approach to the ethical review indeed did not operate from a single philosophical position:

> No, we did not look from one ethical aspect or from one philosophical viewpoint, it was always very broad. And it was also not always separate from societal developments at that moment. But Heeger and the other ethicist, they always brought, not a statement, not like 'I don't find this ethically responsible', but more like posed a discussion statement and on the basis of that statement [we] discussed the experiment further, so that you could weigh pros and cons.[77]

Another interesting point in the documents about the ethical review discussed within the AEC-RIVM is that laboratory animal science quality was included in ethical weighing. While there was consensus within the AEC-RIVM that laboratory animal science and ethical aspects should not be separated, some have pointed towards possible problems because of this. For example, Vorstenbosch and Stafleu listed problems with ethical reviewing in AECs, among which was the difficulty of separating the three types of review (scientific, ethical, laboratory animal science).[78] In 1992, a former AEC-RIVM member wrote a letter to the committee with several tips. One of them was to focus more on the ethical aspects of experiments, as he saw too much attention being put towards technical aspects:

> It is not new, but you should try to discuss more ethically and less technically. How that should be done, I don't immediately know, but I think it would be useful to benefit from Heeger's input and to regularly operate as done during the recent workshops [on ethics]. More attention for discussing a case systematically seems desirable.[79]

Vorstenbosch and Stafleu also listed several other issues with ethical reviewing, including lack of clarity about how to measure suffering. This issue is discussed next.

4.4.2 Suffering?

The registration of animal experiments, required from 1984 onwards, included the registration of the estimated level of suffering experienced by tested animals for each experiment. As we saw in the previous section, an estimation of suffering was also seen as essential for any review by an AEC. The Veterinary Head of Inspection (VHI) provided some instruction for grading animal suffering, which they defined as '[...] the circumstance in which or because of which the health of an animal is compromised or in

76 Boon, Morele Grenzen, 87.

77 Interview Van Iersel.

78 Vorstenbosch and Stafleu, Dierexperimentencommissies in nederland.

79 Letter from Peter Marwitz to RIVM-DEC (29/8/92). RIVM Archive, file no. 1028087.

which pain, injury or other severe discomfort is caused.'[80] Expected suffering was to be graded as mild, moderate, or severe and some examples were given for each level. For example: drawing blood once, killing (without preceding experimental procedures), and gavage feeding were considered mild; frequent drawing blood, cesarean section, and skin transplantation were moderate; long-term deprivation of food, water, or sleep, complete bleeding without general anesthetic (no decapitation), and immunization with complete adjuvant in the sole of the foot were considered severe.[81] Criteria for the grading suffering was not given in the instructions. According to the document, objective criteria for determining suffering does not exist. Rather, such criteria were considered to be a matter of subjective judgement by the individual doing the grading.

In 1990, the CvAvcD created the VHI working group on grading suffering to determine whether the grading system could be improved upon. In 1993, they published their report 'Grading Suffering'.[82] Before discussing the grading system, they reflected on the meaning of suffering. In Dutch, the term *ongerief* is used, which is a bit broader than the English word "suffering". The working group defined it as the antithesis of wellbeing. To clarify their position, they wrote:

> The working group has the position that when an animal is used as a research model, the researcher has the moral duty to ensure that the animals suffer as little as possible. This striving for wellbeing will also result in a higher quality of research. Wellbeing should not be seen as something absolute, but as an optimum that can be reached in the hands of the researcher within the given context of the experiment and the laboratory.[83]

This view of wellbeing fits nicely within the 'scientific mode of care' described by Druglitrø, where care, ethics, and therefore also wellbeing are seen as entangled with scientific practice.[84] Promoting wellbeing is presented here as a win-win for both tested animals and science, which may be precisely because wellbeing is not defined in an absolute sense (in which case not experimenting on the animal would promote wellbeing the most). This contextual approach to suffering and wellbeing is also reflected in the criteria and decision tree developed to grade suffering.[85] In this decision tree, the following criteria were used to determine the level of suffering: induction of pain, deregulation of homeostasis, social isolation, limitation of control over surroundings, general anesthesia, and duration. Following the decision tree would lead to a number between 0 and 9, which in turn indicated mild, moderate, or severe suffering. The criterium 'limitation of control over surroundings' needed to be understood in the experimental context (i.e., the limitations imposed just by being placed in an experimental setting did not count towards the suffering score in this chart). In addition to the deci-

80 VHI, Instructies Registratie Dierproeven, 1984, 28. RIVM Archive, file no. 200047169.

81 Ibidem, 30.

82 VHI, Rapport Gradering ongerief bij proefdieren door de werkgroep gradering ongerief bij proefdieren Veterinaire Hoofdinspectie van de Volksgezondheid, maart 1993. RIVM Archive, file no. 1037927.

83 Ibidem.

84 Druglitrø, Skilled Care.

85 VHI, Rapport Gradering ongerief bij proefdieren door de werkgroep gradering ongerief bij proefdieren Veterinaire Hoofdinspectie van de Volksgezondheid, maart 1993, 13. RIVM Archive, file no. 1037927.

sion tree, the report also contained lists of suffering indicators per species with respect to appearance, feces, behavior, posture, locomotion, and physiology. Some of these indicators are measurable, like weight loss, while others require more knowledge of the animal (e.g., abnormal gait, arched back). Most of the indicators would require what Druglitrø calls 'skillful seeing', an attunement of the senses making it possible to 'read' other animals.[86] The inclusion of 'sad eyes' as an indicator of suffering shows that in the report the authors had not stepped away from the idea that judging suffering is at least partially a subjective practice.

Within the AEC-RIVM, suffering was considered to be part of the laboratory animal science review as well as the ethical review. First, they considered whether the estimation of suffering conducted by the researchers had been correct. In the minutes of the AEC-RIVM, several examples can be found of experiments where the AEC thought that the level of suffering should be estimated higher than the researchers had said.[87] In general, within the RIVM a relatively large percentage of experiments caused high suffering. In 1992, 57% of all experiments were categorized as causing severe suffering, compared to 27% nationally in 1991.[88] This high percentage of severe suffering was in large part caused by the testing of vaccines, which was one of RIVM's important tasks.[89] When presented with an experiment causing high levels of suffering, the AEC would think with the researchers about which measures could be taken to reduce suffering (e.g., pain medication). Van Iersel recalls that this was sometimes a bit of a dilemma when it came to regulatorily required vaccine tests that caused severe suffering: 'Are we doing this right, and should we not think of another way to do this? [...] Can we not assess things in a different way than by using a very uncomfortable animal experiment where death is the only score that you consider while many other elements could have been chosen as a parameter as well.' Of course, developing and validating alternatives was not the task of the AEC, but they could communicate the need for this with the Coordination Point Alternatives to Animal Testing (CAD) of the RIVM, with which they were in contact regularly. After the laboratory animal science aspect had been considered, the expected suffering of the experimental animals could be weighed against the expected benefits of the experiment in the ethical review. As we saw in section 4.3, however, how to do this exactly was a big question mark from the start and continued to be so in the years that followed.

4.5 THE AEC-RIVM AFTER 1997

In this final section, I discuss how things fared from 1997 onwards for the then formalized AEC-RIVM. First, I discuss the experiences with(in) the AEC and how the AEC gradually became an accepted and 'normal' part of the RIVM and later the NVI.[90] I then take a closer look at a few cases

86 See Chapter 6 for examples of attunement in mouse-human interactions.

87 Commissies en werkgroepen RIVM: DEC: relgement en vergaderstukken. Since only some of the AEC minutes were archived, no quantitative statements can be made about how often this occurred. RIVM Archive, file no. 1037880.

88 Jaarverslag Functionaris Ex. Art. 14 WOD RIVM 1996 (11/4/97). Table 4. RIVM Archive, file no. 1035575.

89 Interview Van Iersel. This percentage decreased when alternative vaccine tests were developed causing less suffering and/or using less nonhuman animals (see Chapter 2).

90 In 2003, the AEC moved from the RIVM to the NVI, together with the Animal Research Center.

which caused debate within the AEC and/or between the AEC and the license holder.

4.5.1 Getting started with the New AEC

From 1997 onwards, the AEC of the RIVM was recognized by and operated in accordance with the revised Dutch Animal Testing Act. For formal recognition of the AEC, the law required that there be at least two members independent from the RIVM, including the chair. The AEC-RIVM decided to ask one of the experts on in vitro technologies, Bas Blaauboer, to be the chair of the AEC. He worked at Utrecht University at the RITOX (now IRAS) Institute and was specialized in in vitro toxicology techniques. In that capacity he had supervised and also collaborated regularly with Van Iersel, who by then was working at the RIVM and was asked to be the secretary of the AEC. Since Robert Heeger had already joined the AEC as an external member specialized in ethics, the requirement of two independent members and an independent chair were met when Blaauboer accepted the position of chair.

The AEC was composed of scientists from various background as well as ATs working at the RIVM. According to Van Iersel, the ATs' perspective was valuable, because the AEC not only performed an ethical weighing but also looked at biotechnological aspects of an experiment. It was mostly the ATs that had knowledge about this aspect and could inform other members about the feasibility of biotechnological acts within the context of the experiment. 'This was especially useful, because sometimes experiments were proposed that were just not feasible on a biotechnological level.'.[91] In Van Iersel's experience, the ATs that decided to join the AEC were people that were comfortable with giving their opinion and able to place their knowledge in a wider context. When asked if AEC members were more critical than average, he responded that they were critical thinkers in general but not more (or less) critical towards animal experimentation. When they looked for new members, they did not look for people with a specific opinion on animal testing but rather for people who could contribute to the discussion necessary for performing an ethical review. For this it was also necessary to have people from various areas of expertise. Besides ATs and ethicists, there were also experts representing the field of alternatives. These members tended to be a bit more critical about the use of nonhuman animals, according to Van Iersel. R1[92] remembered there being a critical atmosphere in the AEC, which he related to different perspectives and interests represented in the AEC—from the animal lab to members focusing more on ethical aspect and animal protection. There were however no lay-members or members from animal protection organizations. Van Iersel recalled that the latter had been discussed but that animal protection organizations did not want to join AECs, because this would mean that they would in one manner be cooperating with performing animal experiments. Some of the AEC members, such as Van Iersel, were also members of AECs at other institutes, which allowed for some 'cross pollination'. Overall, however, discussions remained internal.

Both R1 and Van Iersel noticed, albeit from opposite perspectives, that the relation between the AEC and researchers changed in the early days of the formalized AEC. With the new AEC legislation, all researchers performing animal experiments found them-

91 Interview Van Iersel.

92 R1 was interviewed because of his expertise on alternatives, but since he performed nonhuman animal experiments as a researcher during the first years of the formalized AEC, he was also asked about his experiences in that regard.

selves obligated to ask the AEC for permission.[93] This initially caused some apprehension among researchers. R1 had to present his nonhuman animal experiments to the AEC and recalled: 'At first there was, like I said, some mistrust, but that was gone rather quickly, they had understanding for what we were doing. [...] It also really makes that you think well about your experiment, so the AEC really did have a function'.[94] According to Van Iersel, the AEC review gradually became a 'normal' part of doing animal experiments. He also noticed that the quality of the information presented to the AEC improved in his first few years as secretary. Researchers thought more thoroughly about how to conduct the experiment and researched possible alternatives. Because of this, the AEC could perform a better and more realistic review. What helped to improve the quality of information provided was also that it became more common for researchers to speak with AEC members about their experiments while writing the experiment proposal. The obligated of Article 9 course for researchers involved in nonhuman animal experimentation, named after article 9 of the Animal Testing Act, also played a role in this. At first there were many researchers who were given the 'Art. 9 status' based on experience, but as more and more researchers actually took the Art. 9 course, the quality of the proposals that the AEC was receiving began to positively reflect the course's contribution. Researchers' acceptance of the AEC was also influenced by the fact that they hardly ever rejected proposals, instead inviting researchers for a discussion and proposing that certain changes be made. Van Iersel concluded, 'In their totality, discussions in the AEC only contributed to the research becoming better. And everyone benefited from that, including the animals'. R1 agreed and noticed another positive effect of the AEC regarding awareness of alternatives: 'So the AEC really played a role in that, in stimulating and making [people] aware of what was in fact asked by society'. Thus, in general the AEC became an accepted and respected part of the RIVM. This does not mean, of course, that there was never any disagreement about experiments and about the AEC in general.

4.5.2 Points of Discussion AEC-RIVM.

As described in previous sections, the AEC is not an exclusively ethical committee but considers scientific, lab animal science, and ethical aspects of an experiment. Researchers were sometimes resistant to discussing the scientific aspects while presenting their experiment. They expected that they had to justify their experiment on an ethical level, but sometimes they were questioned mostly on the scientific quality of their experiment. According to Van Iersel, this was only logical considering that the AEC consists of many scientists. Additionally, it was important for the ethical review:

> It was more of a discussion about is there enough scientific basis for the experiment, because if (there is) not, it is unethical. So, we turned around the discussion: show us that this is not unethical research because it is scientifically sound. And then we would look if the lab animal science aspects were safeguarded.

Critically reviewing scientific and lab animal quality was thus considered crucial to

93 The RIVM was one of the few institutes where the AEC reviewed on the level of the individual experiment, rather than on the level of a research project (which may contain several experiments) (interview Van Iersel).

94 Interview R1.

the ability to perform an ethical review. The issue of scientific review was also a point of discussion between the AEC and the management of the RIVM as the AEC felt that the scientific review procedure before an experiment was proposed to the AEC was inadequate. In 2001, a scientific test was formalized by the Institutional Council (*Instituutsraad)*. The AEC was pleased with this but not satisfied since the scientific review could be performed by any researcher, including one that had an interest in the research.[95] Instead, they proposed an independent committee that would perform the scientific reviews. This was initially rejected, however, as the administrative burden would be too heavy.[96] But in 2006 an independent Committee of Scientific Review (CWT) was formed, which reviewed experiments before they were proposed to the AEC.[97] About half of the experiments were adjusted based on the CWT-review.[98] The AEC was happy about the formation of the CWT, but it did not stop them from being critical about scientific aspects of experiments. As mentioned earlier, rejection of experiments by the AEC was rare but did happen. Below, I discuss three experiments that caused disagreement either within the AEC or between the AEC and the researcher, each based on a different one of the three reviews: lab animal science quality (3Rs), ethical weighing, and scientific quality (as well as lab animal science). Taking a closer look at these cases can shed some light on the limits of permissibility in the eyes of the AEC-RIVM as well as point towards some more general issues that AECs faced.

Polio Vaccine and Lab Animal Science Quality (3Rs), 2007

This case was discussed extensively in the previous chapter, where we saw how in 1990 the AEC-RIVM began urging researchers to make the switch from monkeys to the Vero cell line to produce the polio vaccine. They kept giving permission for the use of monkeys however, until 2007. Let us now revisit this case from the perspective of the AEC to understand what made them change their view on the permissibility of the use of monkeys for the polio vaccine. By 2007, the production of the polio vaccine was no longer done by the RIVM but by the Dutch Vaccine Institute (*NVI*), and the AEC and animal laboratory had moved there as well. In 2002, the production of polio vaccine for the Dutch market had switched from using monkeys to using cell lines. For the international market monkeys were still used because not all countries had arranged registration of the cell line-based vaccine yet.[99] When, in 2007, permission was again requested for the use of monkeys to produce the vaccine for export, the AEC finally said no.[100] This was not an easy decision; the discussion lasted over a year and there was no consensus within the AEC.[101] Some members felt that they had no choice but to approve the use of monkeys, because otherwise some countries might be without the vaccine. Others felt they could not approve it because an alternative was available, widely used, and accepted. In other words, the experiment did not pass the lab animal science review: the R of Replacement could be applied here and it was not. Practical issues such as reg-

95 Letter dr AJ van Iersel to the Instituutsraad about scientific testing (w. toe.) 8/10/01. RIVM Archive, file no. 2000349279.

96 Letter from A Opperhuizen 8/3/02. RIVM Archive, file no. 2000349279.

97 Adviesgroep Proefdierbeleid. RIVM Archive, file no. 1215.

98 Jaarverslag 2008. RIVM Archive, file no. 1215.

99 DEC NVI verslag 2007. RIVM Archive, file no. 1215.

100 DEC NVI verslag 2007. RIVM Archive, file no. 1215.

101 Interview Van Iersel.

istration, were no reason to give permission for a nonhuman animal experiment that could be done without nonhuman animals. What the AEC did in this and similar cases was to give an end-date to the advice, so that there would be time to arrange practical matters.[102]

The polio case described in Chapter 3 shows the difficult position AECs could be put in. While, in 2007, not giving permission to produce the polio vaccine with monkey kidneys would at worst mean loss of income (in case the buying countries did not manage the licensing of cell-line polio vaccine in time), not giving permission in earlier years would have meant no polio vaccine for the Dutch National Vaccination Program even if technically an alternative existed. All the AEC could do in those years was write letters urging researchers to switch from monkeys to the cell-line.

Syringe Case (Ethical Weighing), 1999

In 1999, the RIVM gave SVM the assignment of starting to use syringes instead of ampoules for the vaccines intended for the National Vaccination Program.[103] Although the new packaging did not differ much from the previous packaging, ICH guidelines stipulated that an extensive stability experiment had to be conducted.[104] If the research design recommended by the ICH had been followed, this would have meant using ten to fifteen thousand nonhuman animals. It would also have included so-called challenge experiments that caused high levels of suffering in nonhuman animals. After discussions between SVM and LGM (the department of RIVM responsible for vaccine quality), the research design was adapted so that 'only' about 3,500 nonhuman animals would be used. The challenge test was deemed unnecessary. A. Vroege of the SVM was invited to discuss the experiments with the AEC. He argued that the use of syringes was not a fashion trend but rather 'a step towards further perfecting the product that is to be made, to prevent the RIVM/SVM from no longer being competitive in the market'.[105] Both economic and societal interests were considered very high, since not using the syringes could lead to losing the National Vaccine Program as a customer and therefore also losing jobs. For doctors, the syringes would also mean more comfort and saving time without added costs. However, it is unclear what the benefit would be for public health. This raised the question of whether or not it was ethically justifiable to use nonhuman animals for human interests that are not concerned with public health but with economics. Does economic interest justify causing suffering in nonhuman animals? Several AEC members did not think so, however a majority did, and the experiment was approved.

Interestingly, the minutes of this meeting start out by saying that because the RIVM has given SVM the assignment to do this, 'factually the choice has already been made'.[106] This statement points to an issue that AECs face as the result of being 'at the end of the chain', a problem also identified by Vorstenbosch and Stafleu.[107] AECs are the last ones

102 Ibidem.

103 SVM is a privatised organisation that performed several tasks for the RIVM that were previously conducted by the RIVM. Later SVM became NVI.

104 ICH is the *International Council for Harmonisation* of Technical Requirements for Pharmaceuticals for Human Use.

105 Minutes DEC 28/4/99. RIVM Archive, file no. 1035580.

106 Ibidem.

107 Vorstenbosch and Stafleu, Dierexperimentencommissies in nederland.

to review an experiment, after it has already gone through several stages of review and approval (such as by funding bodies and the scientific review), putting pressure on the AEC to also give approval. In 1992, the AEC-RIVM suggested to the board of the RIVM that they be involved earlier, from the moment projects were proposed rather than only when individual experiments were submitted to them for review. This was however rejected as potentially causing too much hassle.[108]

This case also shows the difficulty of the ethical review. How could it be decided whether the economic and societal benefits would outweigh the suffering of 3,500 nonhuman animals? What would it mean to take the intrinsic value of nonhuman animals as a starting point in this question?

MAP Case (Laboratory Animal Science and Scientific Quality), 2000–2001

During several AEC meetings in 2000 and 2001, the proposed experiment 'Infection with M. avium ssp paratuberculosis (MAP) in cynomolgus monkeys' was discussed. The researchers who were involved were invited several times to explain their experiment. Researchers designed the experiment to find out whether MAP in cow's milk was involved in causing Crohn's disease in humans, which they suspected to be zoonotic. If the researchers were able to infect cynomolgus monkeys via infected milk, it would be more plausible that Crohn's disease in humans was a zoonotic disease contracted through drinking infected cow's milk. They proposed an experiment with six monkeys, divided into two groups. One group would orally receive a mixture of laboratory grown MAP strains isolated from humans, cows, and deer. The other group was to orally receive cow's milk with MAP. The experiment would start with an operation under full anesthesia, during which a temperature transponder was placed in the abdominal cavity. In weeks five and nine it was planned that the MAP solutions be administered for four days in a row using an oral needle. Throughout a year, the monkeys would be living in an isolator in groups of three and monitored via their feces, blood, skin tests, weight, and temperature.[109]

The AEC acknowledged the high societal relevance of the research, as many people suffer from Crohn's disease and there is no known cure. However, they concluded that the benefit of this experiment did not outweigh the suffering involved for the monkeys. For this they gave two reasons: the species chosen and the scientific design. From a laboratory animal science standpoint, housing monkeys in isolators for a long time is undesirable as it would lead to unwanted stereotypical behavior. Additionally, the infection that the researchers were aiming for would cause diarrhea, which in turn would cause hygiene issues. Long term housing of lab animals in isolated circumstances should be done in animal chambers. However, in this case, permission would not be given for this, due to the safety hazards involved for the animal technicians working with the monkeys. Finally, the AEC cited expected problems with the oral administration of the MAP solutions, given that it would involve catching the monkeys repeatedly.

The AEC also argued that the scientific design lacked epidemiological data to support it. Without information on the chance of infection and the role of genetic predispositions—in combination with the small sample size—the chance of a positive result would be unrealistically small. Chances of a positive result could have been increased

108 Jaarverslag art 14 funct. WOD RIVM 1992. RIVM Archive, file no. 1028254.

109 Proefopzet 200000419. Appendix with a letter from A van Iersel to Gijs Elzinga about: Kennisgeving DEC-advies betreffende proefopzet 200000419. 8/2/2001 RIVM Archive, file no. 2000349279.

by giving the monkeys extremely high doses of MAP but then the process of becoming sick would have been fundamentally different from how it happens in humans and the results would not have been usable. This led the AEC to conclude that 'even a similar experiment with humans would not give useful information'.[110] Furthermore, the design did not allow for falsification of the posed hypothesis. They described the experiment as an 'aimed shot in the dark' and therefore unacceptable.[111] This case was quite clear to AEC members as the scientific quality was simply unacceptable. The researchers subsequently faced a dilemma of how to proceed.

The experiment was rejected three times, but the story was not over yet. On May 29, 2001, AEC chair Bas Blaauboer was approached by J. Nieuwenhuis of the General Management of the Inspection of Commodities (*Keuringsdienst van Waren,* the new name of the VHI*)*, which had commissioned the experiment. He very insistently asked Blaauboer about the experiment. Blaauboer explained the motives for rejecting the experiment, but Nieuwenhuis was not understanding. Nieuwenhuis expressed doubt about the expertise of the AEC-RIVM and said that he could easily have the experiment done elsewhere.[112] Van Iersel recounted the incident to acting DG Gijs Elzinga in a letter, to express the AEC's concern about external influence on RIVM's policy on nonhuman animal experiments. He recalls:

> Well, there was a significant external interest (outside RIVM) in this case as in the one with the [polio] monkeys […] Then it is not surprising that sometimes non-formal ways are used to influence a decision, in this case a government body exceeded its power. But the firmness of our chair made sure that these kinds of actions did not succeed.

The attempt to influence Blaauboer was indeed not successful as the AEC would not budge. The RIVM had one last option: asking the Central Committee of Animal Experiments (CCD) for a second opinion that could overturn the decision of the AEC. Gijs Elzinga considered this option, but Coenraad Hendriksen asked him to reconsider because he felt that the outcome could only be negative for the RIVM and especially the reputation of the institute regarding lab animals. If an experiment is reviewed by the CCD, it is made public in the State Newspaper (*Staatscourant)* and Hendriksen expected that there would be a lot of attention for it if the RIVM decided to do this for two reasons: the use of monkeys and the rarity of CCD reviewing an experiment. Whether or not the CCD approved the experiment, the RIVM would end up losing because they would be seen as an institute trying to push through monkey research.[113] To avoid such publicity, it was decided not to go to the CCD.[114] Instead, the researchers wrote a literature review, concluding that MAP was unlikely to be the sole cause of CD but more likely one of the contributing factors. They recommended further research in humans: 'A good start for establishing the truth about the role of Map in CD would be a proper-

110 Letter from A van Iersel to Gijs Elzinga about: Kennisgeving DEC-advies betreffende proefopzet 200000419. 8/2/2001 RIVM Archive, file no. 2000349279.

111 Ibidem.

112 Memo from Arthur van Iersel to Gijs Elzinga about: Stand van zaken betreffende PO 200000419. 31/5/01. RIVM Archive, file no. 2000349279.

113 Email from Coenraad Hendriksen to Gijs Elzinga on 25/7/01. RIVM Archive, file no. 2000349279.

114 Interview Van Iersel.

ly funded, carefully planned, blinded, international multi-laboratory study with good defined controls and free exchange of agreed optimized methods to detect Map in CD patients'.[115] In this case it was thus a concern about the consequences of the research becoming public, in addition to a stubborn AEC, that stopped the researchers from going forward with the monkey experiment.

4.6 CONCLUSION

In this chapter, we saw how society and politicians demanded more accountability and attention to ethical aspects if acceptance of nonhuman animal experimentation as 'good science' was to continue. Leaving decisions about animal experiments to only the scientists involved in these experiments was no longer seen as acceptable scientific practice. In response to this demand, the government decided to create legislation formalizing AECs. A hefty debate followed about what the content of this new law should be. Scientists and animal protection organizations tried to influence the law on AECs, arguing that their proposal for legislation would lead to the best science, both in terms of scientific quality and moral questions. Scientists were concerned about their ability to continue to do experiments, whilst activists focused on the moral aspect of using nonhuman animals and tried to stress specific ethical views. For the most part, the latter agreed to the scientific mode of care by going along with the idea of AECs (which in principle assumes that animal testing is ethical at least in some circumstances) and did not adopt an animal rights mode of care.[116] This alignment was strategic; they saw it as opportunity to have more impact than they might if they stuck to their strict ideological position of ending all animal testing immediately. While animal protection organizations showed a willingness to compromise by entering into the AEC debate, they were not prepared to join AECs as that would compromise their ideological position too much. Scientists' strategies focused on pointing out the catastrophic consequences of the activists' proposals, as well as their "emotional" rather than rational basis. In addition, they proposed alternative legislation which seemed to accept the demands of society, but in which all control over the ethical review was kept with insiders. The resulting legislation was a compromise and while it included some of the measures that scientists at first argued would be catastrophic for Dutch science, over the years AECs became an accepted part of scientific practice.

Where scientists seemed satisfied with the AECs outsiders remained critical, as became clear in the 2005 evaluation by Freriks et al. AECs give approval to experiments and as such legitimize nonhuman animal experiments, giving them a 'stamp of good science'. But what is the meaning of AEC approval if experiments are almost never rejected and the ethical review is either skipped or based on inconsistent ethical perspectives? And, returning to the question posed in the introduction, what is the meaning of the AEC system in general for the lives of nonhuman animals? Based on the experiences

115 A.A.P.M. Herrewegh, P.J.M. Roholl, P. Overduin , J.W.B. van der Giessen and D. van Soolingen, 'Is There Evidence for a Link between Crohn's Disease and Exposure to Mycobacterium Avium Ssp. Paratuberculosis? A Review of Current Literature 230086001', 2004. <https://www.rivm.nl/bibliotheek/rapporten/230086001.html>, 46.

116 Druglitrø contrasts the animal rights mode of care with that of the scientific mode of care. While in the latter, ethics is considered within the context of the scientific practice of animal experimentation, the former rejects animal experimentation outright.

with the AEC-RIVM, it seems that AECs mostly have preventive effects that improve the scientific and laboratory animal science quality of nonhuman animal experiments. Additionally, while experiments were hardly ever rejected, AECs did regularly request adaptations. This certainly had a great impact on individual lives of tested animals, for example when suffering was reduced by refinement measures proposed by the AEC or when less nonhuman animals suffered because researchers looked more critically at their research designs.

Within the scientific mode of care perspective, where human and animal interests are understood interdependent, AECs seem to benefit both humans and tested animals. But if we step outside of this perspective that leaves many aspects of nonhuman animal experimentation unquestioned and attempt to view AECs from a non-anthropocentric perspective, we can see that on a more fundamental level AECs further cement nonhuman animal experimentation as a form of good science. Likewise, they seem to reproduce unequal interspecies power relations by not questioning the anthropocentrism underlying the practice of animal experimentation and the one-directionality of the 'ethical weighing'. This underlying anthropocentrism is not only expressed in the content of the legislation, but also in the AEC-system, since this is based on the idea that it is up to humans to make decisions about the lives of other animals. Within this system, there is no space for dissenting voices that do not adopt the scientific mode of care. So, while AECs may have had positive effects on the lives of tested animals, on a more fundamental level, they only consolidated the subordinate position of nonhuman animals. If they also functioned to make nonhuman animal experimentation more acceptable to society, they may actually have slowed down developments which moved away from anthropocentrism, which would be undesirable, at least from the perspective of tested animals.

THE XPA-MICE

A story in two parts

THE XPA-MICE: A STORY IN TWO PARTS[1]

The XPA-mouse model is one of many transgenic mouse models that have been developed since the late 1980s, when scientists first learned how to create such models. Transgenic techniques rapidly became popular in the international scientific community, promising to make mice that were 'just like humans' in all relevant ways. This meant that nonhuman animal testing would no longer be limited by issues of interspecies translatability, thus doing away with scientific critiques of using mice and other nonhuman animals as stand-ins for humans.[2] The new, presumably more relevant models sometimes also promised to reduce nonhuman animal testing by being more effective testing objects than "regular" nonhuman animals, allowing for smaller sample sizes. This was also the rationale behind developing the XPA-knockout mouse, the protagonist of the following chapters.

The first viable XPA-knockout mouse was created at the Utrecht University Medical Center by Annemieke de Vries and colleagues in 1994, in collaboration with the Dutch National Institute for Public Health and Environment (RIVM).[3] XPA-knockout mice were genetically engineered to be deficient in DNA-repair with the idea that this would make them suitable as a model for testing carcinogenicity. For decades, pharmaceuticals and chemicals had been tested for carcinogenic effects with the "two species chronic bioassay". For any given substance, a test would use up to a thousand mice and rats and last between two and three years.[4] Alternative tests using transgenic mice (e.g., XPA-mice) were expected to require only a quarter of the mice and last only a quarter of the time, thus reducing both nonhuman animal use and costs.

In the following two chapters, I will tell the story of the XPA-mice from beginning to end. The first part focuses on the broader story: why were these mice created and why do they no longer exist? In the second part, I zoom in on the 'laboratory choreography' of mice, humans, and materials. To understand this choreography, I also reflect on broader mice-human relations by focusing on the legal position of mice versus humans.

1 Parts of Chapters 5 and 6 have been published previously in Anne van Veen, 'The Life of an XPA-Mouse. A Posthumanist Approach to Becoming with Humans in Laboratory and Law', TRACE ∴ Journal for Human-Animal Studies, 6.1 (2020), 26–51 <https://doi.org/10.23984/fjhas.78050>.

2 David Resnik, Ethical Issues Concerning Transgenic Animals in Biomedical Research, in J.R. Garrett ed., *The Ethics of Animal Research: Exploring the Controversy* (Cambridge, MA, 2012) 169-179

3 A. de Vries, 'Carcinogenesis in XPA-Deficient Mice' (Universiteit Utrecht, 1997).

4 Denise E. Robinson and James S. Macdonald, 'Background and Framework for ILSI's Collaborative Evaluation Program on Alternative Models for Carcinogenicity Assessment', Toxicologic Pathology, 29.1_suppl (2001), 13–19 <https://doi.org/10.1080/019262301753178438>.

CHAPTER FIVE

Part One: From the First to the Last XPA-Mouse

CHAPTER 5: PART ONE: FROM THE FIRST TO THE LAST XPA-MOUSE

5.1 INTRODUCTION

The XPA-mouse's story starts off as a success. As De Vries and team expected, the XPA-mice were found to be more sensitive to carcinogens, leading to a publication in *Nature* in 1995.[1] Soon after, the XPA-mice were included in the large international validation program ACT in which American, Japanese, and European researchers joined forces to find an alternative carcinogenicity test. Transgenic mice were 'hot' and seen as potentially the most important innovation in carcinogenicity testing since the Ames test.[2] Thousands of XPA-mice were bred in Bilthoven and shipped all over the world for validation testing. By 2001, carcinogenicity assays using transgenic mice, such as the XPA-mouse, had been approved by the FDA. RIVM researchers anticipated great international interest in their mouse, estimating a market of millions, and started to investigate ways of marketing the XPA-mouse to companies that were required by law to perform carcinogenicity testing on their products (from here on, these companies are referred to as 'industry'). However, as promising as this all sounds, not a single XPA-mouse was ever used for the purpose of regulatory carcinogenicity testing. This leads us to the main question of this chapter: what drove the development of the XPA-mouse model and how can the lack of implementation of the model be explained? To answer this question, we will follow the XPA-mouse, or rather the thousands of XPA-mice that were bred, from their initial creation to the final mouse being frozen in a repository.

This multispecies story can only be understood within the more general context of developments in usage of transgenic nonhuman animal "models". Not just the XPA-mouse, but transgenic mice models in general never made the breakthrough in carcinogenicity testing that was expected and the chronic bioassay is still practiced today.[3] Moreover, rather than reducing nonhuman animal testing, it is likely that transgenic techniques have led to an *increase* in nonhuman animal use. Schuppli, for example, has shown that in the UK nonhuman animal testing increased between 1999 and 2000 and that this increase was mainly due to the use of transgenic nonhuman animals.[4] However, transgenic issues were not the only cause of XPA-mice use being held back. Two

1 Annemieke de Vries and others, 'Increased Susceptibility to Ultraviolet-B and Carcinogens of Mice Lacking the DNA Excision Repair Gene XPA', Nature, 377.6545 (1995), 169–73.

2 Letter form CF van Kreijl, H van Steeg, A. Opperhuizen to G Elzinga and G de Mik. 24/2/1997; Bespreking op 26/2/1997 short term carcinogeniteits assay m.b.v transgene muismodellen, RIVM Archive, file no. 5042. The Ames test was introduced in 1973 by Bruce N. Ames as new assay for evaluating carcinogenicity using four mutant strains of Salmonella to show mutagenic effects of substances. Angela NH Creager, Soraya Boudia, and Nathalie Jas, 'The Political Life of Mutagens: A History of the Ames Test', Identifying Mutation, 2014, 285.

3 Although not as much as in previous decades, since its limitations are now well recognized, especially in relation to the carcinogenic potential of chemicals. Miriam N. Jacobs and others, 'Chemical Carcinogen Safety Testing: OECD Expert Group International Consensus on the Development of an Integrated Approach for the Testing and Assessment of Chemical Non-Genotoxic Carcinogens', Archives of Toxicology, 94.8 (2020), 2899–2923 <https://doi.org/10.1007/s00204-020-02784-5>.

4 Catherine A. Schuppli, David Fraser, and Michael McDonald, 'Expanding the Three Rs to Meet New Challenges in Humane Animal Experimentation', Alternatives to Laboratory Animals: ATLA, 32.5 (2004), 525–32.

barriers to validation and implementation of alternatives that played important roles in the polio vaccine case again appear on the stage here, namely: risk aversion and regulations. Finally, we will see that international harmonization and competition were additional important themes. While both drove innovation when commercial parties invested in academic research, the latter at other times could stifle progress when patents prevented worldwide use of certain models.

This chapter begins with a sketch of the historical background of transgenic mice (inter)nationally and at the RIVM. I then describe how the first XPA-mouse was made (Section 5.3) and evaluated as part of an international validation program (Section 5.4). Section 5.5 centers around reasons for the XPA-mice not being used for carcinogenicity testing and the final section (5.6) relates what happened to the XPA-mice after the end of the evaluation program.

5.2 HISTORY OF TRANSGENIC MICE

Adapting mice for scientific purposes started long before the use of transgenic techniques. In the early 20th century, inbreeding and selection were used to 'standardize' laboratory animals and adapt them to the needs of scientists. The aim was to create homogeneous batches of rodents, sometimes with specific characteristics, such as a high tumor incidence. A well-known example is the Wistar Rat developed in the US by the Wistar Institute in 1906 and sold all over the world as 'the rat you can count on'.[5] In the Netherlands, the first inbred rodent line, a mouse line, was created by the Dutch Cancer Institute in 1937.[6] In the 1970s, the development of recombinant DNA techniques opened the door to further possibilities of adapting nonhuman animals to the desires of scientists, and mice were again the animal of choice to try these new techniques on. These new techniques combined with other new developments in isolating and working with embryonic stem cells made creating transgenic animals possible in the 1980s.[7]

The first transgenic mouse models developed were 'oncomice', mice with an activated oncogene that were therefore more prone to develop tumors than "regular" mice. Hanahan describes how several researchers in the US were working on different oncomice independently from one another.[8] One of these researchers was Philip Leder at Harvard University who developed the myc-mouse—the first oncomouse (and animal) to be patented. Leder's research was financially supported by the DuPont Corporation with six million dollars. In exchange, DuPont was entitled to exclusive licensing rights on the patented oncomouse, while the patent remained with Harvard. This type of collaboration between industry and academia became more common in the 1980s, when industry saw the commercial potential of academic research in the field of molecular

5 Bonnie Tocher Clause, 'The Wistar Rat as a Right Choice: Establishing Mammalian Standards and the Ideal of a Standardized Mammal', Journal of the History of Biology, 26.2 (1993), 329–49 <https://doi.org/10.1007/BF01061973>.

6 Ontwikkeling van de Proefdierkunde in Nederland., ed. by Gulden, W.J.I. van der & Gaalen, J.M. van (Eds.).

7 Allan Bradley and others, 'Modifying the Mouse: Design and Desire', Bio/Technology, 10.5 (1992), 534 <https://doi.org/10.1038/nbt0592-534>.

8 Douglas Hanahan, Erwin F. Wagner, and Richard D. Palmiter, 'The Origins of Oncomice: A History of the First Transgenic Mice Genetically Engineered to Develop Cancer', Genes & Development, 21.18 (2007), 2258–70 <https://doi.org/10.1101/gad.1583307>.

biology and closer connections were formed between the two domains.[9]

Both academics and various interest groups in the general public criticized the patent being awarded to Harvard. Researchers were unhappy with the broad scope of the patent, which was not given for the myc-mouse specifically, but for a 'non-human eukaryotic animal whose germ cells and somatic cells contain an activated oncogene sequence introduced into the animal, or an ancestor of the animal, at an embryonic stage.'[10] They were concerned it could be interpreted as a patent on any genetically modified animal more prone to develop tumors. Indeed, DuPont went on to lay licensing claims on many different transgenic nonhuman animals, to the dismay of scientists who developed these other tumor-prone rodents. They claimed that DuPont's aggressive licensing approach held back the use of transgenic nonhuman animals as institutes were unwilling to enter into licensing agreements with DuPont.[11]

The general public was opposed to the patent as they felt that 'life' should not be patented. Protest came from religious organizations as well as animal advocacy groups, who feared that such patents would lead to a devaluation of life.[12] For four years after the oncomouse patent, no further animals were patented as, according to Marshall, there was an unofficial moratorium.[13] This moratorium was short-lived however, as three patents on animals were granted in 1992 and forty-seven were granted in 1997.

When Harvard and DuPont applied for a European patent on their oncomouse in 1989 at the European Patent Office, they were met with similar objections. A protest campaign was organized in which 300 NGOs, religious organization, and political parties joined forces. The protesters described the oncomouse is a 'Trojan mouse': 'The Onco-Mouse is presented as a useful invention to mankind; however, it also opens the door to patent almost every life form from now on. The Onco-Mouse is actually a Trojan mouse'.[14] Despite protests, the patent was awarded in 1993.

One of the intended applications of these first oncomice was testing the carcinogenic and mutagenic effects of chemicals.[15] At the time, scientists tested the carcinogenicity of pharmaceuticals and chemicals with a two-species (rats or mice) chronic or lifetime bioassay. The test used large numbers of mice and rats, took a long time (up to three years), was expensive, and was often not a good predictor for carcinogenicity in humans (with

9 Sasha Blaug, Colleen Chien, and Michael J. Shuster, 'Managing Innovation: University-Industry Partnerships and the Licensing of the Harvard Mouse', Nature Biotechnology, 22.6 (2004), 761–63 <https://doi.org/10.1038/nbt0604-761>; Daniel J. Kevles, 'Of Mice & Money: The Story of the World's First Animal Patent', Daedalus, 131.2 (2002), 78–88. Toine Pieters, Interferon: The Science and Selling of a Miracle Drug (Routledge, 2005), xxi.

10 Philip Leder and Timothy A. Stewart, 'Testing Method Using Transgenic Mice Expressing an Oncogene', 1999 <https://patents.google.com/patent/US5925803A/en> [accessed 10 March 2021].

11 Blaug, Managing Innovation, 761.

12 Eliot Marshall, 'A Deluge of Patents Creates Legal Hassles for Research', Science, 288.5464 (2000), 255–57 <https://doi.org/10.1126/science.288.5464.255>.

13 Ibidem.

14 Inter Press Service, Europe: Offensive Launched Against Patenting a "Trojan Mouse" (Brussel, 1993). http://academic.lexisnexis.eu/?lni=3SPF-P5R0-001G-V412&csi=280434&oc=00240&perma=true.

For more on the protests, see Anne van Veen, 'De Muis van Troje', Ex Tempore, 37.3 (2018), 244–57.

15 Kevles, Of Mice and Money.

false positives being a problem).[16] An alternative test was therefore highly desired.[17]

In the Netherlands, researchers at various universities and institutes were also working on developing transgenic mice models. A 1991 Health Council report on transgenic animals mentioned the following research areas as being most important: cancer research (including carcinogenicity), immunology, hereditary diseases, pharmaceuticals.[18] In response to these new transgenic techniques, guidelines and regulations were developed which required special permission for the use of genetically modified organisms (animals or plants). To regulate this, the government established the Temporary Committee on Genetic Modification (*VOCGEM*), which wrote the first guidelines in 1990.[19] The RIVM was one of the Dutch institutes interested in developing TG-models and in connecting to international developments in these areas.[20] One of the institute's focus points was finding an alternative way of testing carcinogenicity using a TG mouse model. As the RIVM did not have the facilities to create a TG mouse line, collaboration with other institutes was required. In the late 1980s and early 1990s, the RIVM, Utrecht University, and the Dutch Cancer Institute collaborated to develop the emu-pim-1 mouse model, a mouse with an activated pim-1 oncogene.[21] When these mice turned out not to respond as desired, attention was turned to other transgenic mice models that might be more suitable. One of these models was the XPA-knockout mouse. [22]

5.3 THE FIRST XPA-MOUSE

'As you may already know, I made that mouse', is what Annemieke de Vries wrote to me in reply to the email I sent her inviting her for an interview about the XPA-knockout mouse. She was working at the RIVM as an intern for Harry van Steeg when the institute became interested in developing a transgenic mouse model as an alternative for the two-year chronic bioassay. Safety testing of chemical substances was part of the work of the RIVM and, like many others in the business, they also felt the need for a more sensitive test that would be more informative, quicker, and would use fewer nonhuman animals.[23] After the pim-mouse did not respond with the desired results, they turned their attention to two other mouse models: the methyltransferase (mt-)mouse and the DNA-repair deficient XPA-mouse. De Vries started her PhD in September 1992 and

16 Fanny K. Ennever and Lester B. Lave, 'Implications of the Lack of Accuracy of the Lifetime Rodent Bioassay for Predicting Human Carcinogenicity', Regulatory Toxicology and Pharmacology, 38.1 (2003), 52–57.

17 Robinson & Macdonald, Background and Framework.

18 Beraadsgroep Genetica van de Gezondheidsraad, Het belang van transgene dieren voor medisch biologisch onderzoek (Den Haag, 1991) 11-13.

19 Ontwikkeling van transgene dieren voor carcinogeniteitsonderzoek, GGO, RIVM Archive, file no. P1192.

20 Letter from J.G. Vos to B. Sangster 'Betreft samenwerking RIVM-RUU op het gebied van transgene muizen/ratten', 29/05/1990, RIVM Archive, file no. 6260.001/2226 9A2-5.

21 Letter from C.F. van Kreijl (LCM) to H. van Loveren (PAT) 'Re: Gebruik transgene dieren', 17/05/1990, RIVM Archive, file no. 6260.001/2226 9A2-5.

22 Harald Teeuwen, Bezoekverslag Taconic Farms, Inc., 31/01/2002, Dossier, RIVM Archive, file no. 1059244/2000338582. These studies showed increased sensitivity to carcinogen-induced tumors. However, further experiments demonstrated that the emu-pim-1 mouse model only works well with carcinogens that target the lymphoid system.

23 Interview De Vries.

worked together with research technician Conny van Oostrom in creating these mice under the supervision of Harry van Steeg. The mt-mouse turned out to be very difficult to make and while De Vries worked on that, Van Oostrom was asked to get started on the XPA-mouse. When progress was made with making the XPA-mouse, De Vries also turned her attention to this mouse model.[24] According to Van Oostrom, Van Steeg had his heart set on a DNA-repair mouse, stemming from his earlier work on DNA-repair together with Jan Hoeijmakers at Erasmus University.

The team was specifically interested in Nucleotide Excision Repair (NER). NER is one of the major types of DNA-repair and is involved in removing various types of DNA damage, such as damage caused by UV-light.[25] It consists of two pathways: Transcription Coupled (or TC-NER) and Global Genome (or GG-NER). In humans, several diseases are caused by an inherited defect in the genes involved in NER. Of these diseases, Xeroderma Pigmentosum is the only one that leads to a predisposition to developing cancer. People who have this illness develop tumors when exposed to sunlight (among other symptoms). Importantly, people with XP can live long lives when not exposed to carcinogens such as UV-light. Van Steeg and the team therefore thought that a mouse model with similar DNA-repair defects would have a low incidence of spontaneous tumors but a high tumor response to carcinogens, making it more suitable for carcinogenicity testing then oncomice and their high incidence of spontaneous tumors.[26] All of the XP-genes (XPA-XPG) except for XPV are somehow involved in one or both pathways of NER, but patients with a defect in the XPA gene display the lowest NER activity of all (virtually none).[27] De Vries mentioned two more reasons for choosing XPA.[28] Firstly, XPA patients mainly developed skin tumors, which were easily visible in laboratory situations. Secondly, different research groups internationally were investigating mice with different XP-gene complex knockouts, but not yet on XPA (or so the Dutch team thought). The Japanese research group of Tanaka and co-workers had published about the human XPA-gene and cloning a human and murine DNA repair gene that complemented the defect of group-A xeroderma pigmentosum (known as XPA Correcting or XPAC gene). Detailed information about the structure and nucleotide sequence of these genes was not available, however. Therefore, the XPAC gene had to be isolated and characterized before a construct could be made to create an XPA-knockout mouse.[29]

Before the work on this construct could begin, the team had to find collaboration partners at a university with the facilities to actually make transgenic mice. The UMCU had such facilities, was conveniently located nearby, and was willing to collaborate. With the collaboration in place, Van Oostrom could start her work on isolating and mapping the murine version of the XPA gene. This was a rather practical endeavor, involving a lot of 'old fashioned manual labor (*handwerk*)', as Van Oostrom put it.[30] She would start early in the morning, developing films of blots of sequence gels and hope that 'spots' or 'bands' would develop on one of them to indicate the desired result has

24 Interview Van Oostrom.

25 Harry van Steeg, 'The Role of Nucleotide Excision Repair and Loss of P53 in Mutagenesis and Carcinogenesis', Toxicology Letters, 120.1–3 (2001), 209–19; De Vries, Carcinogenesis.

26 De Vries, Carcinogenesis; interview De Vries.

27 Ibid. XPV is involved in post-replication repair.

28 Interview De Vries.

29 De Vries, Carcinogenesis.

30 Interview Van Oostrom.

been found. Van Steeg meanwhile tended to come in just as the results were ready, quickly pulling them out of the machine to see if they had been successful. Van Oostrom did not appreciate her boss taking off with the results after all her hard work: 'I am not some "pipetting goat"'.[31] All in all, however, they all look back on their team as being really close—more like friends than colleagues—with the occasional friendly banter.[32]

The XPA gene is a rather large gene and sequencing it took a while, finding several pieces of DNA separately before the whole gene was complete.[33] Once Van Oostrom had managed to completely sequence the gene, she continued on to create a construct which she and De Vries subsequently used to knockout the XPA gene in mouse embryonic E14 stem cells (provided by the Netherlands Cancer Institute) using gene targeting techniques. Colonies of these cells were picked and screened for homologous recombination of the targeting construct.[34]

De Vries then froze these colonies of ES-cells. She first defrosted the ES-cells—which was another exciting moment in the TG-mouse making process, as they had to hope that the cells would 'turn back on' again.[35] Luckily, in this case, this posed no problem and they could subsequently proceed to the next step, injecting the ES-cells into blastocysts of the mouse strain C57Bl/6. The blastocysts were obtained by injecting female mice with hormones, so that they would go into cycle. After a few days, the mice were killed to harvest the blastocysts. De Vries then implanted these blastocysts, containing both E14 and C57Bl/6 ES-cells, into 'pseudo-pregnant' C57Bl/6 mice.[36] After implantation, an anxious wait followed to see if they had been successful. Successful transmission of E14-derived germ cells could easily be recognized, as it gave offspring an 'Agouti' coat color, with different coat patches having different pigmentation levels. These chimeric mice would then be mated with regular C57Bl/6 mice to give XPA heterozygous, non-chimeric mice.

When her colleagues returned to the RIVM after the holidays, De Vries was waiting for them with a reason to celebrate. It turned out that she had quickly genotyped these newborn mice over the holidays, showing that some of them were the XPA-heterozygous mice that the researchers had been hoping for. These mice could then be used to breed homozygous XPA-knockout mice.[37]

The "mouse-making" process was again a lot of 'handiwork' and a technically challenging procedure that went wrong regularly. An important difference for De Vries between the RIVM and the UMCU was that in Utrecht researchers were expected to handle tested animals themselves, whereas at the RIVM only animal technicians were allowed to perform nonhuman animal testing procedures. Thus, here the mouse-making procedures were done by De Vries herself, giving a very literal meaning to 'I made that mouse'.

31 Ibidem.

32 Interviews Van Oostrom & De Vries.

33 Conny Th M. van Oostrom and others, 'Cloning and Characterization of the Mouse XPAC Gene', Nucleic Acids Research, 22.1 (1994), 11-14.

34 Exons 3 and 4 of the XPA gene were deleted by replacing them with a PKG-NEO battery through homologous recombination. As NEO, makes the cells Neomycin resistant, antibiotics could be used to separate the cells with PKG-NEO from the other cells. About 2% of the recombination had been homologous (meaning success). De Vries et al., Increased Susceptibility.

35 Interview Van Oostrom.

36 De Vries et al., Increased Susceptibility; interview De Vries.

37 Interview Van Oostrom.

De Vries recalled being very proud to have the XPA-mice finally walking around and ready for testing, but some disappointing news awaited her. When attending a course for PhD students in Stockholm, she heard from other researchers that a Japanese research group had also made an XPA-mouse. 'Initially we were very disappointed'.[38] But what else was there to do besides continuing the research? It was no longer enough to just make an XPA-mouse in order to publish, they now needed to demonstrate that the mouse model was more sensitive to certain substances and UV-light, like humans with type A XP.[39] The Dutch researchers therefore quickly collected enough mice for experiments to test their sensitivity to UV-B and 7,12-dimethylbenz(a)anthracene (DMBA).[40] First, embryonic fibroblasts were tested in vitro, which demonstrated extremely low cell survival of XPA-/- cells compared to both XPA+/- and XPA+/+ cells, which behaved similarly. After the in vitro experiment, mice of all three genotypical variations were used in four additional in vivo experiments of exposure to UV-B or DMBA, with an acute (one week) and a short-term (14 weeks) study for each compound. As both UV-B an DMBA affect the skin (and DMBA was applied to the skin), the mice were shaved weekly. Twice a week, the mice were checked for tumors and tumor-bearing mice were killed. Within a week, the acute effects such as crust formation and epidermal hyperplasia of both UV-B and DMBA were noticeable in XPA-/-mice. In the other types of mice, these effects were completely absent, thus showing the increased sensitivity of the skin to genotoxins such as UV-B and DMBA. After six weeks, UV-B effects on the eye became visible, such as lesions (see Figure 5.1). Because almost all XPA-/- mice had developed eye lesions after 14 weeks of exposure, exposure was discontinued at that moment. Overall, the short-term experiments showed a higher incidence of tumors and increased sensitivity in XPA-/- mice.[41]

These results were considered worthy of publication and in 1995, the article 'Increased susceptibility to ultraviolet-B and carcinogens of mice lacking the DNA excision repair gene XPA' was published in *Nature*. The same issue also contained an article entitled 'High incidence of ultraviolet-B-or chemical-carcinogen-induced skin tumors in mice lacking the xeroderma pigmentosum group A gene' by Nakane et al., the Japanese research group that had been working on the same mouse model.[42] Both articles being published back-to-back in *Nature* meant that neither of the two research groups had to be disappointed. According to De Vries, the two groups' similar findings likewise meant that the two articles strengthened one another, like a sort of ultimate replication (AdV). In the Dutch article, the value of the XPA-mouse was described as follows:

> These models will not only be very suitable to study the relationship between the XPACgene, repair capacity and mouse phenotype, they also can be used in short term carcinogenicity assays, to more quantitatively assess the potential risk of DNA repair defects (homozygous/ heterozygous) in terms of cancer predisposition.[43]

38 Interview De Vries.

39 Interview De Vries.

40 Interview Van Oostrom.

41 De Vries et al., Increased Susceptibility.

42 Hironobu Nakane and others, 'High Incidence of Ultraviolet-B-or Chemical-Carcinogen-Induced Skin Tumours in Mice Lacking the Xeroderma Pigmentosum Group A Gene', Nature, 377.6545 (1995), 165–68.

43 De Vries et al., Increased Susceptibility, 14.

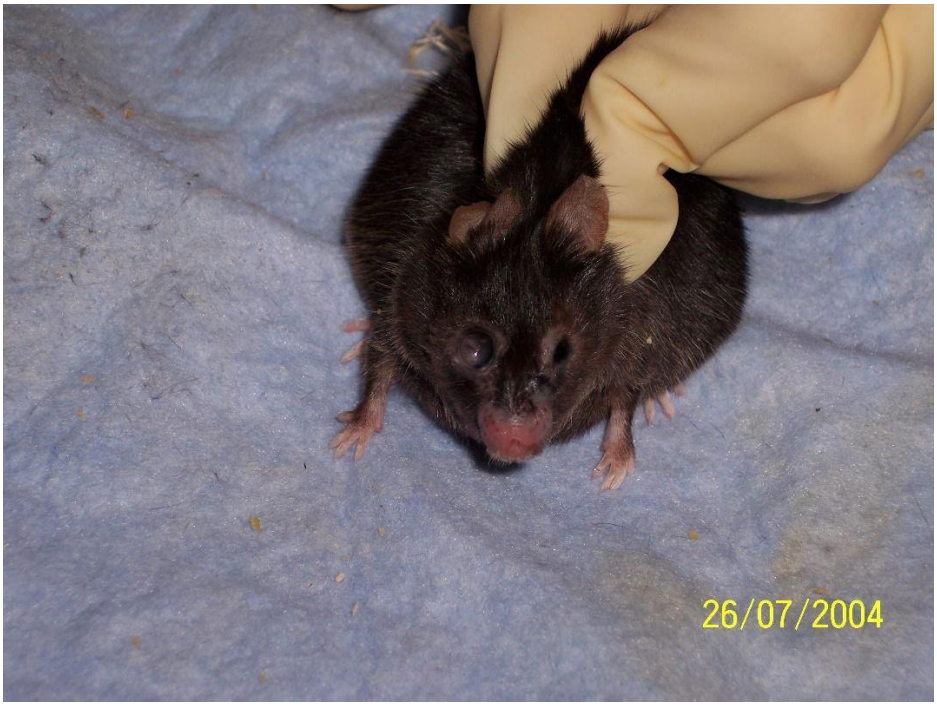

Figure 5.1 XPA-mouse with eye lesion. Source: RIVM.[44]

While the study had shown sensitivity to compounds that led to skin tumors, less was known about the development of internal tumors in XPA-mice and humans. Therefore, to further demonstrate the value of the XPA-mouse model as a carcinogenicity assay, the researchers needed to conduct a study with a compound that would induce internal tumor formation. They selected Benzo(a)pyrene, as it is known to induce 'bulky' DNA adducts (a type of DNA damage repaired by NER). In addition, they studied spontaneous tumor formation in ageing XPA-mice. The twenty-two XPA-/- mice in the ageing study were all still alive after eighteen months. At that point they killed them, and histopathological analysis showed that one mouse had a lung tumor and four mice had liver tumors, whereas none of the wild mice had tumors. All tumors were benign and had developed after fifteen months of age, confirming the expected low spontaneous tumor incidence in XPA-mice for at least the first year and a half of their lives. These and other studies also demonstrated a striking difference between humans and mice with XPA. While humans with this disease also suffer from severe neurological abnormalities, such abnormalities were never observed in the mice. An explanation for this was not found.

The B(a)P-study involved exposing mice of all three genotypes to gavage-feedings of the Benzo(a)pyrene dissolved in soy oil. The mice were treated this way three times per week for thirteen weeks and then observed for twenty-six weeks. At the end of the

44 This image is from a later study with XPA-mice and ageing. De Vries has confirmed that the eye-lesion in this image is the same type of eye-lesion that occurred in the study with UV-B and DMBA. A similar image can be found in De Vries, Carcinogenesis. I have chosen to include this image, because the image quality is much better.

experiment, more XPA -/- mice had developed tumors than the other two genotypes, showing increased sensitivity to internal tumor-inducing compounds as well. From these results, the potential of the XPA-mouse as an alternative carcinogenicity assay was clearly demonstrated to De Vries and colleagues. The following advantages were listed at the final page of De Vries' thesis: less time is needed, less animals are needed, and lower doses can be used that are more relevant to actual human exposure. 'A main future aspect will be the validation [...].'[45]

So far, the XPA-mice's story was running smoothly: De Vries and team had managed to create viable mice that showed the expected and desired sensitivity towards tumor-inducing compounds. In addition, the potential of the mouse was recognized and shared with the international community in a *Nature* publication. As we have seen in previous chapters, however, showing potential is only the first step and by no means a guarantee for successful implementation. As De Vries already mentioned in her thesis, the next step was to be validation.

5.4 VALIDATING THE MOUSE

The mouse chronic bioassay that De Vries and team (as well as other scientists worldwide) were looking to replace was used to test carcinogenicity and required by law for both pharmaceuticals and chemicals before they were allowed onto the market. This meant that for the XPA-mouse test to be accepted as an alternative for the chronic bioassay, regulations would have to be changed. These regulations varied between countries and since pharmaceuticals and chemicals were often brought onto the market internationally, regulations would have to be changed worldwide.[46] This situation did not apply to just the XPA-mouse test but to all new tests that were designed to be part of safety regulations. These differences in regulations were not only impractical for those wishing to bring products onto the market but also seen as undesirable by scientists and regulators. In response to this, international harmonization of regulatory testing became an important focus of the safety testing community during the 1990s.[47] In 1990, the pharmaceutical industry and regulatory agencies in the US, Japan, and Europe jointly started the process of evaluating and harmonizing testing requirements for pharmaceuticals, including carcinogenicity testing.[48] This process took the form of International Conferences on Harmonization for the Technical Requirements for the Registration of Pharmaceuticals (also known as the ICH). The ICH was an advisory body, leaving decisions about safety testing regulation to be the responsibility of individual countries and the EU.[49]

In 1996. the ICH Safety Working Group acknowledged the potential of new carcinogenicity models such as transgenic mouse models and proposed to replace one of the two bioassays with a short- or medium-term alternative. Although regulators and the

45 De Vries, Carcinogenesis, 126.

46 For example, if a company wants to bring a substance onto the market in ten countries and even one of these countries still requires the mouse chronic bioassay, there is no point in using the XPA-mouse test.

47 Michael D. Waters, Dave Allen, and Mike D. Waters, Reducing, Refining and Replacing the Use of Animals in Toxicity Testing (Royal Society of Chemistry, 2013).

48 Robinson & Macdonald, Background and Framework.

49 'ICH Official Web Site : ICH' <https://www.ich.org/>.

international pharmaceutical testing community were interested in changing testing practices, there was also general agreement that more information was needed about potential alternative models. According to ACT steering committee member Denise Robinson, this prompted International Life Sciences Institute (ILSI) and the Health and Environmental Sciences Institute (HESI) to form the Alternatives to Carcinogenicity Testing Committee in 1996 and start the ACT program, with the aim of evaluating possible alternative models.[50] From the beginning, a global focus by ACT was considered crucial, since the models were to be used globally and required global regulatory acceptance.

ILSI/HESI in the US teamed up with the Central Institute for Experimental Animals (CIEA) in Japan. Because they were aiming for international acceptance of their alternative tests, they were keen to find a European partner as well. Having heard about the XPA-model's potential (and these being the only potentially suitable mice already 'walking around' in Europe), they approached Harry van Steeg and asked him and his team to join the program. An international evaluation program was exactly what the Dutch team and their XPA model needed, so they were eager to join—as Van Steeg put it, 'one and one is three, very easy to say yes'.[51] Yet while saying yes might have been easy, finding enough European partners to realize all the experiments would prove to be a challenge. In the section that follows, I will first consider how the XPA-mouse was framed as a European mouse to garner enough European support and partners to conduct all the required experiments. I will then focus on the experiments conducted at the RIVM as part of the ACT program. Finally, we will see what happened when the program ended and how the XPA-mouse was evaluated.

5.4.1 A European Mouse in the ACT Program

The ACT program ran from 1996 to 2001 and was initiated and coordinated by ILSI/HESI. The program was a 'partnership among industry, government, and academic scientists' with the overarching goal to 'evaluate the ability of these new models to provide useful information for human cancer risk assessment'.[52] The public-private partnership was considered important for the program to build both a strong foundation and scientific consensus about the usefulness of the models. Forty-eight industry laboratories, seven government and research laboratories, and nine scientific advisors participated in the program. Together they tested twenty-one substances in six in vivo models and an in vitro Syrian Hamster Embryo assay. The transgenic mouse models tested were: p53 and TG.AC in the US, rasH2 in Japan, and XPA and XPA/p53 in Europe. Working group assays were formed for each model, with the RIVM chairing the XPA working group and Coen van Kreijl of the RIVM participating as a scientific advisor.

Despite enthusiasm on both sides, the XPA-mouse model's (and therefore Europe's) participation in the program hung in the balance for a while. The program was designed to test twenty-one substances in all the models. To achieve this, the XPA working group had to find partners to spread out the workload and costs. While partners were easy to find in the US and Japan, in Europe this proved more difficult. Jan van Benthem,

50 Robinson & Macdonald, Background and Framework.

51 In Dutch 'one and one is three' is één plus één is drie, This expression is used to indicate that collaborating yields more results than not collaborating (in case of not collaborating, one and one would be two). Interview Van Steeg.

52 Robinson & Macdonald, Background and Framework, 1.

senior scientist at the RIVM Health Protection Research Laboratory, was involved with ACT from the beginning and recalls:

> The idea was to test one or two substances ourselves and have other interested parties such as universities and industry do the rest, but they were really difficult to find. We gave them the mice, but they had to pay the rest themselves and very few people were willing to collaborate under those conditions.[53]

The RIVM launched a European initiative to get more laboratories involved in evaluating TG mouse models and specifically the 'European' mouse model XPA. They emphasized that participation was important in order for Europe to keep up with international developments in the US and Japan.[54] According to Van Steeg, everyone wanted to participate as transgenic models were 'hot' and new, and the goal of developing a new carcinogenicity test was shared by all. Yet when asked specifically about industry participation, he also remembers the European industry being less enthusiastic than industry in Japan and the US. He characterized them as having a mixed attitude. On the one hand they did not want to "miss the boat", but on the other hand they were conservative and not all that concerned about the chronic bioassay and the many nonhuman animals used for it. For RIVM researchers, however, reducing nonhuman animal suffering was an important motivation on top of improving safety testing.[55]

Interested parties were found within the Netherlands, as well as in Germany, Denmark, France, and Belgium, but the response of the European pharmaceutical industry (EFPIA) was disappointing, and financial support in the form of a grant deemed unlikely. In December 1996, Coen van Kreijl described the situation as being at a 'go/no go point'.[56] The motivation to participate was very strong among RIVM researchers. In a letter to the board, they wrote that this could be the most important innovation in carcinogenicity testing since the Ames test.[57] Participation was not just about developing a new test however, but was also seen as beneficial for the international position of the institute. Within the RIVM, leading the European part of the program was considered to be an opportunity to strengthen the institute's international position and reputation. In addition, it was expected that a TG mouse model would lead to a fourfold decrease in use of experimental animals and a dramatic reduction of costs for the industry. In a letter from the head of the pharmaceutical's laboratory to the board, the following reasons for participation were given:

> First, we can score internationally with the validation of a TG-mouse test based on development research at our institute. Second, there is the possibility to, within the competition between experts and countries,

53 Interview Van Benthem.

54 C.F. van Kreyl and H. van Steeg, Identification of potential carcinogens in short term bioassays using DNA deficient transgenic mice, i.e., the XPA transgenic mouse model, 1996, RIVM Archive, file no. 5042.

55 Interviews Van Benthem, Van Steeg, De Vries.

56 Letter from C.F. van Kreijl, 'Follow-up of "european initiative on evaluation and validation of transgenic mouse models for short term carcinogenicity testing", 05/12/1996, RIVM Archive, file no. 5042.

57 Letter form CF van Kreijl, H van Steeg, A. Opperhuizen to G Elzinga and G de Mik. 24/2/1997. Bespreking op 26/2/1997 short term carcinogeniteits assay m.b.v transgene muismodellen., RIVM Archive, file no. 5042.

strengthen knowledge and contacts to increase chances for future rapporteurships. Third, it can show that the Pharmaceuticals Laboratory and their staff have added value.[58]

As we can see, participation was not only regarded as beneficial for the institute as a whole, but also for specific departments within it. Altogether, the ACT program was too good an opportunity to decline and they decided to pursue the program, even though there were not enough partners to test all twenty-one substances. After the program had already started, some funding was found outside of industry from the Platform Alternatives for Animal Testing (PAD). PAD funded two studies in collaboration with TNO with 100,000 guilders per year for three years to test the compounds D-mannitol and Phenacetin.[59] Within the European division of ACT, the RIVM was responsible for breeding and distributing the XPA-mice used in the experiments. In addition, several of the substances were tested at the RIVM.

5.4.2 The ACT Experiments

To validate the XPA-mouse model as a model for carcinogenicity, experiments were conducted in which groups of XPA-mice were exposed to known carcinogens and non-carcinogens. Additional control groups of XPA-mice were not exposed. In other countries, different mouse models were being tested in a similar way. Before the experiments commenced, a subcommittee of the ACT program developed standardized protocols to ensure comparability between models when the studies were complete. These protocols stipulated (among other things) that in all studies: male and female animals should be used, three experimental groups receiving different dosages and a negative control group should be included, and a full histopathological analysis should be performed.[60] In addition, each participating laboratory was required to demonstrate that they could elicit a positive response from the model they were testing, with human carcinogens known to give a positive response in said model. For the XPA-mouse, this was either B[a]P or 2-AAF (B[a]P had already been tested at the RIVM as part of De Vries' thesis). The compounds for testing in the ACT experiments were selected based on the following characteristics: existing data from male and female rat and mouse two-year bioassays; established toxicology database of in vitro and in vivo data on mode of action; data related to human exposure and effect; and nonproprietary and multisource. The twenty-one compounds selected were: genotoxic human carcinogens: cyclophosphamide, melphalan, phenacetin; immunosuppressant human carcinogen: diethylstilbestrol, estradiol; rodent carcinogens/putative human noncarcinogens (based on human data: phenobarbital, clofibrate, reserpine, dieldrin, methapyrilene; rodent carcinogens/putative human noncarcinogens (by mechanism): haloperidol, chlorpromazine, chloroform, metaproterenol, WY-14643, DEHP, sulfamethoxazole; noncarcinogens: ampicillin, D-mannitol, sulfisoxazole.[61]

The following compounds were tested on XPA-mice at the RIVM, in addition to the UVB, DMBA and B[a]P already tested: Cyclosporin A, Phenacetin, Resperine, D-manni-

58 Letter from J.W. Dorpema to Directie RIVM, 'Project geneesmiddelen en transgene dieren', 24/09/1996, RIVM Archive, file no. 5042.

59 Letter from R.A. Woutersen (TNO) to PAD, W.A. de Leeuw, 17/04/1998, RIVM Archive, file no. 1060245.

60 Robinson & Macdonald, Background and Framework.

61 Ibidem, 18.

tol, PhIP, p-cresidine, and 2-AAF.[62] Despite standardized ACT protocols, experiments were sometimes adapted based on experiences in research practice and unexpected responses from mice. In 1998, the research designs for tests with XPA-mice were adjusted, lengthening the treatment period from twenty-six to thirty-nine weeks and adding two weeks of treatment-free time before killing the mice[63]. The reason for this was that a twenty-six-week period seemed to be too short to induce tumors in XPA-mice. In a study with PHiP, XPA-mice who received the highest dose were in such bad condition after a few weeks that they were removed from the experiment and doses were lowered.[6465] After a few experiments with XPA-mice, the researchers considered that crossing XPA-mice with p53 mice might result in an even better model. Thus, double transgenic mice were bred and from then on included in the program.

5.4.3 The End of ACT

The ILSI/HESI ACT program ended in 2001 with the publication of a 351-page supplement to the 29th Volume of the *Journal of Toxicologic Pathology*. The supplement included discussion of all study results, evaluation of the program, and description of future perspectives. No one model stood out from the rest as *the* model to be used from now in substitute for the mouse bioassay. All models were found to have their limitations and, according to Jay Goodman, 'the belief that we will one day have a perfect model (e.g., a "humanized" rodent) is a fallacy'.[66] In evaluating the evidence of the models, the XPA, XPA/P53, rasH2 and p53 models were found to be of similar value, providing similar types of information.[67] In an article about the XPA and XPA/P53 models evaluation, however, Van Kreijl et al. reached a slightly different conclusion: 'Nevertheless, the overall results described in this paper clearly indicate that of both DNA repair–deficient models studied, the XPA/p53 model appears to be the most suitable candidate model for short-term carcinogenicity testing.'[68] Van Steeg echoed this sentiment.[69]

The ACT steering committee deliberately spoke about evaluation of the models and

62 All compounds tested in Europe: TNO Nutrition, Netherlands: R. Woutersen, B. Lina, J. Bruintjes (Haloperidol, Phenacetin, Reserpine, D-Mannitol); RIVM, Netherlands:J. van Benthem, R. Beems, H. van Steeg, C. van Kreijl (Cyclosporin A, Phenacetin, Reserpine, D-Mannitol); Solvay, Netherlands: M. de Haan, R. Thoolen (Haloperidol); Scantox, Denmark: P. McAnulty, M. Skydsgaard (DES, WY-14,643); DVFA/IT, Denmark: I. Sorensen, A. Mortensen, V. Aarup (DEHP); Boehringer Ingelheim, Germany: A. Kalkuhl, P. Stei (Clo brate); Janssen Pharmaceuticals, Belgium: A. Vynckier, K. van Deun, J. Vandenberghe (Phenobarbital); Notox Ltd., Netherlands: J. van der Hoeven, S. de Hoog (Phenobarbital); AstraZeneca, Sweden: R. Fransson-Steen, I. Paulson (WY-14,643); Pzer, France: L. Longeart, G. Hanton (Sulfamethoxazole); CIT, France: R. Forster, C. Fabrequettes (Ampicillin); Sano -Synthelabo, France: N. Roome (Ampicillin); Organon NV, Netherlands: H. Joosten, M. Steenhof, H. Dreef, M. Tegelenbosch (Estradiol). Van Kreijl et al., Xpa and Xpa/p53.

63 R. Beems, Six months oral carcinogenicity study with Cyclosporin A in XPA -/- mice, 02/06/1998; Amendement voor proefopzet (9800518 en 9800603). Volgnummer 3 08/09/1998, RIVM Archive, file no. 650080/9800518.

64 R.B. Beems, Korte rapportage pathologie, Carcinogenicity of PhIP in XPA -/- mice, 26/03/1998, RIVM Archive, file no. 199600363.

65 Bepaling van de carcinogeniteit van PhIP in XPA deficiente muizen en de relatie met DNA-adduct vorming en mutatie-inductie in diverse organen, Project 650090, RIVM Archive, file no. 199600363.

66 Jay I. Goodman, 'A Perspective on Current and Future Uses of Alternative Models for Carcinogenicity Testing', Toxicologic Pathology, 29.1_suppl (2001), 173–76, 173.

67 Ibidem.

68 Van Kreijl et al., XPA and XPA/p53, 126.

69 Interview Van Steeg.

not about validation, as they thought it was too soon for that. In Dutch articles and AEC applications however, validation was mentioned regularly alongside the aim to 'find a new test' to replace the mouse bioassay. Although validation was not the official goal of ACT, the transgenic mouse model assays that were evaluated have been accepted by the FDA and written into ICH guidelines (though they have not been made obligatory).

While not everyone agreed on the value of the different models, one thing that everyone seemed to agree on was that the process of collaboration had been a great success. This was so much the case that Robinsons wrote: 'Beyond the data, the collaborative process by which the models were evaluated may also represent a prototype for assessing new methods in the future.'[70] De Vries described the process as 'the way it should always be' and other respondents agreed that the collaboration had been open and pleasant.[71] Van Benthem recalled that 'collaboration was very smooth; we were with many people and would meet once a year in the US and twice a year with the European group to see what needs to be adjusted or changed'.[72]

The XPA-mouse model was seen as a great success, not only because of its potential as a carcinogenicity assay but also because of what it meant for the RIVM and individual careers. Through developing the mouse strain, the institute had become part of a larger international research program, which in turn led to more visibility and more research opportunities. For Van Steeg, this determined basically his whole career.[73] Yet when I asked respondents about the actual use of the XPA-mouse model, answers were not so optimistic, varying from 'I hope so' to 'I doubt it'; 'I can't imagine so', to 'No, they are not used for carcinogenicity testing'.[74] Hence, while the XPA/P53 was FDA approved and even seen as the most promising model by some, it was never actually used for its intended purpose. Why this was so is the focus of the next section.

5.5 ON WHY THE XPA-MICE WERE NOT USED AS INTENDED

As we saw in Section 5.3, the main reason for creating the XPA-mouse model, was to find an alternative model for testing carcinogenicity of both pharmaceuticals and other chemical substances. Despite the mouse model being seen as a great success in some respects, the XPA-mouse is not and has not been used for regulatory testing of carcinogens. In this section we look at possible reasons as to why the XPA-mouse was never used for the purpose it was initially created for. Different respondents recalled different possible reasons for this—sometimes overlapping, sometimes complementary, and sometimes contradictory. No one pointed at one decisive factor that prohibited the use of the XPA-mouse but respondents speculated about different barriers relating to both characteristics of the assay and circumstantial factors. In the following sections, I will discuss barriers to the use of the XPA-mouse assay relating to: the XPA-mouse itself, the evaluation research, marketing and patent issues, and the questionable need for an alternative in the first place.

70 Robinson & Macdonald, Background and Framework, 19.

71 Interview De Vries.

72 Interview Van Benthem.

73 Interviews Van Oostrom & Van Steeg.

74 Interviews De Vries, Van Oostrom, Van der Laan, and Van Steeg.

5.5.1 The XPA-Mouse Itself

Respondents and the evaluation report both mentioned shortcomings of the XPA-mouse model. First of all, there were doubts as to whether or not the XPA model would be able to detect non-genotoxic substances given that the model is based on DNA-repair deficiency.[75] Since genotoxins are usually detected by the genotoxicity assay (which happens before the carcinogenicity assay), there was a greater need for a model that would also detect non-genotoxins. Secondly, the XPA-mouse was very sensitive to toxins, meaning that doses that would normally be used in assays cannot be used, because they would kill the mice (as happened in the PhiP experiment discussed earlier).[76] To overcome these problems, researchers later suggested that the XPC mouse would be a better model, as it was less sensitive to toxins and appeared to detect non-genotoxins as well.[77] By the time the XPC mouse model was considered, however, the ACT program was already over and there was not enough money to really go anywhere with it.[78]

Thirdly, the compound Phenacetin was found to be negative in the XPA-mouse model, even though it was classified as a human genotoxic carcinogen. Phenacetin was negative in TgAC and p53 as well, leading to discussion about the genotoxicity of the compound, which is positive in the Ames assay for genotoxicity.[79] Although the XPA-mouse assay was found to do an overall better job than the mouse bioassay and the genotoxicity of Phenacetin was questioned, a potential false negative was seen as a bigger problem than false positives. This is because in this case a false negative could entail risk to the public if a human carcinogen were to go undetected. According to De Vries, risk aversion makes it difficult to implement alternatives: 'If you like to stay on the safe side, rather ten unjustified accusation [false positives], well that is what you also see in society of course, if something happens, we do not want to run that risk, then you have the whole society on your case (*valt over je heen*)'.[80]

Lastly, a difficulty was mentioned that relates specifically to the XPA/p53 model. RIVM scientists considered this model to have even more potential than the XPA model. However, it was also hard to breed and expensive due to being a double transgenic model, especially when compared with the p53 mouse model, which was a heterozygous transgenic model and therefore easier to breed than both XPA and XPA/p53.[81] Another reason that the p53 may have been favored was that it was an American model.[82] Despite the shortcomings of the XPA model, it seems unlikely that these were the decisive factors in the non-use of the XPA-mouse, since other models also had shortcoming and the evaluation report didn't describe any one model to be obviously better than others.

75 Syril D. Pettit, 'Panel Discussion on the Application of Alternative Models to Cancer Risk Assessment', Toxicologic Pathology, 29.1_suppl (2001), 191–95 <https://doi.org/10.1080/019262301753178618>.; Interview Van der Laan.

76 Joost PM Melis and others, 'Detection of Genotoxic and Non-Genotoxic Carcinogens in Xpc-/- P53+/- Mice', Toxicology and Applied Pharmacology, 266.2 (2013), 289–97.

77 Ibidem; Interviews Van der Laan & Van Steeg.

78 Interview Van der Laan.

79 Samuel M. Cohen, 'Alternative Models for Carcinogenicity Testing: Weight of Evidence Evaluations Across Models', Toxicologic Pathology, 29.1_suppl (2001), 183–90 <https://doi.org/10.1080/019262301753178609>.

80 Interview De Vries.

81 Interview Van Steeg.

82 Interview Van Steeg.

5.5.2 The Evaluation Research

We saw before that it was much harder to find (financial) partners for participating in the ACT program in Europe than in the US and Japan. As a consequence, only thirteen substances were tested with the XPA-mouse, compared to twenty-one with the other models. The other models had also been tested more extensively before the start of ACT, making the gap in available data even larger. In addition, in studies with the XPA-mice, the treatment duration was changed from six months to nine months when the research process was already in progress, and the positive control compound changed several times (from B[a]P to p-cresidine to 2-AAF). This meant variation between studies, making it difficult to compare them and to draw firm conclusions. On December 13, 2001, the ICH held a meeting at the EMEA in London to discuss the New Methods in Carcinogenicity Testing of Medicinal Products.[83] During this meeting, all the mouse models in the ACT were discussed and advice was given about their regulatory acceptance.[84] EMEA toxicologist Peter Kasper had reviewed the data about the XPA and XPA/p53 models and was rather critical about the research that had been conducted to that point, not recommending them for regulatory acceptance. With regard to the XPA model, he wrote: 'As the number of compounds tested is limited we have considered the other data too (including the compounds used as positive control). Mephalan and cyclophosphamide have not been tested. As a whole the set of data is insufficient. The model is promising, but cannot be recommended for the moment'.[85]

With regard to the XPA/p53, he expressed:

> The protocol with which the XPA-p53 has been used is inadequate. Only one dose has been tested, which is the same dose level as the high dose for the XPA (tested in parallel). The number of compounds (only 10) is too small to draw conclusions. The sensitivity of the double transgene might be higher than the XPA only. Also this model might be promising, but further evaluation is important.[86]

The ICH did recommend the p53 and H2Ras model for regulatory acceptance and in both cases the large number of compounds being tested was mentioned as a reason for this recommendation.[87] Van der Laan, the chair of the meeting, recalls the Safety Working Party of the ICH 'just not being impressed by the XPA story'.[88] He characterizes the research as 'too academic' with too much experimentation (e.g., changing duration), in contrast to the studies with p53 and Rash2 where there had been more discipline in sticking to standardized protocols.[89]

Although the regulatory agencies did not differentiate between the mouse models in regulatory acceptance (the FDA has approved all ACT mouse assays), a recommenda-

83 The EMEA is the European Union Agency for the Evaluation of Medicinal Products now known as EMA.

84 Report from the Meeting on the New Methods in Carcinogenicity testing of Medicinal Products on 13/12/2001, London, 04/02/2002.

85 Ibidem, 3.

86 Ibidem, 3.

87 Safety Working Party, CPMP SWP Conclusions and Recommendations with regard to the use of genetically modified animal models for carcinogenicity assessment, London, 07/06/2002.

88 Interview Van der Laan.

89 Ibidem.

tion by the ICH to prefer p53 and H2Ras over the XPA-mouse could of course still have affected the choices that the industry made. As we will see next however, the choice for XPA was never available to industry.

5.5.3 Marketing and patent issues

Despite the aforementioned ambivalence towards the value of the XPA-mouse model and the validation research, the RIVM still had full confidence in the potential of the XPA/p53 model, as evidenced by the following statements: 'The model has just been validated with good results, is accepted as state-of-the-art worldwide and is now ready for commercialization by SVM'[90] and 'RIVM desires that the mice and products derived from them be developed and utilized to the fullest extent so the benefits can be enjoyed worldwide by the 'biomedical and toxicological research community and the general public.[91]

In June 2001, Gerrit de Mik, Department Head of Risks, Environment, and Health, wrote a letter to the board letting them know that international interest had been expressed in both the XPA and XPA/p53 mice and that the market was estimated to comprise several millions (whether this referred to mice or guilders was not specified).[92] The RIVM found itself confronted with the question of how to go about making these mice available to the market. This was not a straightforward question: breeding and selling nonhuman animals on a large scale was not part of their usual business and there were patent issues that needed to be resolved.[93]

The main reason the mouse had to be exploited commercially was that this would be the only way to make these mice available for industry. While it was possible to provide them for academic research on a non-profit basis, this was not allowed in the case of for-profit corporations. Another reason was that selling the mice with a profit would allow the institute to earn back the large sum of money that it had invested, estimated to be millions in resources and labor power.[94]

Bringing the mouse model onto the market meant dealing with companies that held patents over (parts of) the mice. As we saw before, DuPont held a very broad patent on all oncomice, including the XPA mouse. The usage rights for the particular p53 gene construct which had been utilized, meanwhile, was held by Taconic Farms, a commercial breeder of experimental animals.[95] In the late 1990s, negotiations had already started with Taconic about collaborating to bring these mice onto the market, but these conversations ended in 1998 because the RIVM refused to acknowledge DuPont's patent over the XPA-mouse and was considering fighting DuPont's patent claim in court.

90 SVM Position Paper, (n.d.), 2, RIVM Archive, file no. 1059244. The SVM was the Foundation for furthering public health and environment (Stichting ter bevordering van de Volksgezondheid en Milieuhygiene), mainly involved in vaccine supply for the RIVM and export, but an agency with its own mandate and some space to pursue other (monetizing) activities (phone conversation former director of SVM).

91 Draft License agreement with Taconic about XPA-knockout mice, 20/03/2002, RIVM Archive, file no. 1059244.

92 Letter from G. de Mik (director Sector Risico's, Milieu en gezondheid) to board RIVM Re: transgenic mice. 13/06/2001, RIVM Archive, file no. 6260.001.

93 Ibidem.

94 SVM Position Paper, (n.d.), RIVM Archive, file no. 1059244.

95 Email from Harald Teeuwen to Donna and Sam (Taconic), Subject: XPA-mouse available to academia?, 28/05/2002, RIVM Archive, file no. 1059244.

Van Steeg remembers receiving a letter from DuPont claiming licensing rights to the XPA and XPA/p53 mice: 'We received a letter from DuPont, that made no sense at all. [...] has caused a lot of commotion and RIVM spent quite some time on it, deploying the state attorney'.[96] He could also see the positive side of it for him personally: 'the good news for me was, I was taken completely seriously all of a sudden. I could do whatever I wanted, they had never seen this, that it was really seriously on the market and not some hobby'.[97] Despite efforts by the legal department, RIVM did not win the fight with DuPont. By 2001, the patent position of Dupont was too strong to be denied, with the company holding the patent in the US (renewed for seventeen years in 1998), Japan, and EU. Reopening negotiations with Taconic and DuPont was therefore considered the only option.[98]

De Mik presented three options for the board to discuss:

1. 'Selling and breeding mice ourselves (profit per mouse more than fl.500 [€227] per item)
2. Having a commercial company breed and sell the mice, with a payment to the RIVM.
3. Signing over the right to breed and sell the mice to a company for a one-time payment.'[99]

The board of the RIVM discussed the letter and came to the decision to move forward with making the mice commercially available, provided that it this were in cooperation with Taconic and Dupont. The reasons given for advising in favor of marketing the XPA-mouse were:

1. It suits the national/international position of the RIVM to bring new technology (better and more animal friendly) onto the market.
2. [We] invested in this and this way the investment can be earned back in a suitable manner.
3. The capacity (staff and housing) of the CDL (Central Animal Laboratory) is underused.[100]

Taconic was interested in doing business with the RIVM provided that the institute refrain from legal action. The board did not want to enter into a legal battle and so negotiations with Taconic were reopened. In the mid-1990s, Taconic made an agreement with DuPont to sublicense the TG.AC mouse model and four additional models. The p53 was also sublicensed and in 1998 the rasH2 and K6/ODC followed, while negotiations were underway to sublicense XPA as the final model. In January 2002, Harald Teeuwen, the business manager of external relations for SVM, visited Taconic Farms in the US as part of his assignment to find an acceptable agreement with Taconic. His report about

96 Interview Van Steeg.

97 Ibidem.

98 Harald Teeuwen, Bezoekverslag Taconic Farms, Inc., 31/01/2002, RIVM Archive, file no. 1059244.

99 Letter from G. de Mik (director Sector Risico's, Milieu en gezondheid) to board RIVM Re: transgenic mice, 13/06/2001, RIVM Archive, file no. 6260.001.

100 Email from Gijs Elzinga to Gerrit de Mik, subject: transgene muizen 12/07/2001, RIVM Archive, file no. 6260.001.

Taconic from the visit was very positive. He described it as a family business which stood out for its warm and familiar atmosphere, breathing calmness and stability—a place where people enjoy working. After the visit, SVM started working on a draft license agreement, hoping it would be ready soon as an order had already come in for a shipment of XPA/p53 mice. In April 2002, Organon requested a quote and a sale offer was made for 156 'pieces' of XPA/p53 mice—50% female, 50% male, 4–7 weeks old—at an estimated price of $45, 240 (excluding VAT).[101]

Negotiations did not run smoothly, however, and many emails were sent back and forth between RIVM, Taconic and DuPont. With little to no progress, the RIVM and SVM reconsidered their options and concluded that only the following two roads could be taken:

1. Only work with DuPont and breed the mice at the RIVM.
2. Work with both DuPont and Taconic and have Taconic breed the mice.[102]

Only the second option met the minimal conditions established by the SVM, which excluded scenarios in which the RIVM was involved in large-scale commercial breeding. They gave several reasons for the exclusion of this scenario. Firstly, they saw such a breeding program as potentially damaging to the reputation of the institute because it had the potential to result in stories (whether true or false) being spread about "experimental" or "production" animal suffering. Secondly, involving a specialized breeding company such as Taconic was seen as a way to supply the world with experimental animals in an "animal friendly" way. Thirdly, they thought SVM should focus on its main tasks related to public health, and commercial breeding would not have fit well within this focus. In interviews, several respondents also mentioned that commercial activities were not suitable for a government agency such as the RIVM, whose focus is public health. As De Vries put it 'We as RIVM are not on earth with a commercial purpose'.[103] In the end, they stated that even if they would have been willing to get into the business of commercial breeding, they would never have been able to compete with commercial breeders.[104]

A few days after options had been reconsidered, Teeuwen emailed Veerman the next 'move in the chess game with DuPont': sending them a letter in which they explained why the RIVM did not want to be involved operationally, making collaboration with DuPont impossible without Taconic involved as the mouse breeder.[105] Indeed, such a letter was sent to Dupont, explaining that they were not prepared to get involved in the breeding of XPA-mice. The letter also stated that the RIVM had contacted potential end-users (i.e., industry) and that they 'invariably expressed pronounced dislike of the business concept [as proposed by DuPont]'.[106] The letter ended with a paragraph about what the RIVM would do if negotiations failed:

101 Letter from M.F.A. Veerman (director SVM), P. de Vrey (head CDL), H.W.A. Teeuwen (manager external relations) to S.C.M. de Hoog (Organon, Toxicology of drug disposition), 16/04/2002, RIVM Archive, file no. 1059244.

102 Letter from Thijs Veerman (SVM) to H.A.P.M. Pont (RIVM) Vermarkting transgene muismodellen RIVM (XPA en XPA-P53), 11/3/2002, RIVM Archive, file no. 1059244.

103 Interview De Vries.

104 Ibidem.

105 Email Harald Teeuwen to Thijs Veerman, 'Brief naar Dupont' 2002, RIVM Archive, file no. 1059244.

106 Letter from Thijs Veerman to DuPont, 27/03/2002, RIVM Archive, file no. 1059244.

> If this [collaboration with Taconic] proves to be not feasible, either because RIVM and Taconic cannot reach agreement, or because this route to commercialization is blocked or frustrated by DuPont, RIVM will refrain from commercialization of its transgenic mice strains altogether and intends to clearly communicate the reasons for such a decision to the biomedical and toxicological scientific research community worldwide.[107]

Despite Teeuwen's strategic move and strong wording, an agreement was never reached, and the XPA-mouse never became available commercially. There are no documents indicating a flat-out refusal by one of the parties and no such refusal was recalled by interviewees either. It seems more likely that negotiation efforts ceased after failing to reach successful conclusion over time.[108]

5.5.4 Questionable Need for an Alternative

The XPA-mouse was created to serve as an alternative for the chronic mouse bioassay that was performed in addition to a chronic rat bioassay. Prior to the start of ACT, the industry was already questioning the added value of the mouse bioassay and suggesting it could just be left out, but it remained required by regulations. Goodman also wrote in his ACT evaluation report that in dealing with pharmaceuticals, often the rat bioassay in combination with toxicokinetics and genotoxicity tests would be enough and that the mice bioassay could usually be left out without replacement.[109] Only in situations in which the genotoxicity tests were inconclusive could a TG mouse model assay be of additional value. There were were hardly any carcinogenicity testing of chemicals performed in the EU as these were only deemed necessary when mutagenicity and genotoxicity are deemed insufficient.[110] Based on these tests, a carcinogenicity risk profile could usually be calculated. According to Van Benthem, these calculations could also have been made in the 1990s, but no one looked to them because 'nobody worried about 100 rats more or less'. Van Der Laan recounts a story pinpointing the issue:

> I said that the two-year mouse bioassay is nonsense, has too little scientific value, so we can really just get rid of that. And someone said: but if you do allow transgenic mice studies now, then what would be the meaning of that, that would then also not have any value right? And I have never been able to give an answer to that.

The value of the mouse bioassay seems not to have been in the information it gave, but in that it made a company comply with regulations that did not allow leaving it out. The same can then be said for a TG mouse model assay, when this assay is only performed to comply with regulations.

Overall, the alternative TG mouse models did not make the breakthrough that was expected, and their informative value is questionable, except perhaps in specific situa-

107 Ibidem.

108 Interview Van Benthem.

109 Goodman, A perspective on current and future uses.

110 Jan van Benthem, 'The Effect of REACH Implementation on Genotoxicity and Carcinogenicity Testing', RIVM Report 601200008, 2008; interview van Benthem.

tions when other tests raise questions. As of 2020, the FDA and ICH are considering if a new approach to evaluation of pharmaceuticals can make the rat bioassay obsolete as well. For the XPA-mouse, it seems that even if marketing efforts had been successful, chances were small the mice would have been used very often.

5.6 THE LAST XPA-MOUSE

The end of ACT did not mean the end of the XPA-mice at the RIVM. In 1998, Van Steeg was again approached by Americans with an interest in the XPA-mouse, this time for participation in an NIH funded research program on ageing. The research program consisted of basic research into the role of DNA repair in ageing. Even though the RIVM's focus had always been applied research, they were glad to participate in this project as it allowed them to stay close to groundbreaking research.[111] Participation entailed more than just supplying mice; the RIVM became involved as the "animal core" of the research. According to researcher Martijn Dollé, this was because of the excellent non-human animal facilities at the RIVM. Other strains of transgenic mice were brought to the RIVM as well, all with different NER deficiencies.[112] These mice were put in cages in groups of four and put on either standard feed or restricted calorie diets. They then watched the mice to see how they aged, ideally sending them to a pathologist just before they died. Animal technician Piet de With recalls this being quite challenging in the beginning.[113] Together, the ATs and researchers trained in recognizing signs of impending death, such as significant weight loss, hair standing up straight, dull coat, sitting in a corner, et cetera. In the early years of this research program, it became clear that XPA-mice did not age much faster than wild type mice, with the main difference being that they developed more tumors.[114] Using mice with a long lifespan in ageing research meant high expenses, which did not make XPA-mice very suitable for this type of research. The ERCC1 mouse model was chosen instead for further research, as mice from this strain age much faster than wild type mice. Even though the XPA-mouse model was no longer used, the RIVM continued to be significantly involved in the ageing research project until March 2019. As of 2021 the RIVM has a small role in the NIH ageing project researching mutations in the genome of human blood cells.[115]

In addition to research into ageing and alternative carcinogenicity testing, XPA-mice have been used in a variety of other non-regulatory studies. Many of these studies were basic research studies conducted at universities with XPA-mice supplied by the RIVM. About eight years ago, the RIVM ceased its breeding and supply of XPA-mice. The XPA-mice can now be found frozen at a repository of the NIH, but respondents agree that it was unlikely that the mice would be used again in the future and definitely not for regulatory research. According to Van Benthem, transgenic mice have turned out to be more

111 Interview Dollé. Martijn Dollé participated in the Ageing research project, first as a researcher from Harvard and later at the RIVM.

112 Ibidem.

113 Interview De With.

114 Martijn E. T. Dollé and others, 'Increased Genomic Instability Is Not a Prerequisite for Shortened Lifespan in DNA Repair Deficient Mice', Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 596.1 (2006), 22–35 <https://doi.org/10.1016/j.mrfmmm.2005.11.008>.

115 Email correspondence Dollé.

valuable for basic research than for regulatory carcinogenicity research, where they never made the expected break through. Yet if we look back at the AEC applications and reasons for participating in ACT, reducing numbers of nonhuman animals used in regulatory testing was the main rationale for developing and testing the XPA-mouse. This is a more general issue, which Resnik discusses as a main ethical issue concerning the use of transgenic animals in research.[116] Transgenic animals are often developed with the idea that they will reduce nonhuman animal testing, thinking that they can be used more efficiently and effectively. The truth of this is questionable however. Schuppli has shown that, in the UK, nonhuman animal testing increased between 1999 and 2000 and that this increase was mainly due to the use of transgenic animals.[117] There are several paths that can lead to such an increase: the use opens new areas of research, many nonhuman animals are needed to develop and maintain breeding colonies, and developing transgenic animal strains is inefficient. In the Netherlands, a striking increase in what is called 'animals killed in stock' was signaled by the Veterinary Head Inspection (VHI) in 1997 and again by the National Committee advise on Animal testing policy (NCaD) in 2015.[118] Both pointed to the use of transgenic animals as the main cause of the rise in numbers of nonhuman animals killed in stock, which in 2013 even exceeded the number of nonhuman animals that were tested on.[119]

For the RIVM, reducing nonhuman animal testing is still an important goal, but the institute no longer looks to transgenic mouse models to achieve that. Breeding transgenic models has ceased completely and the focus has shifted towards humane and stem cell research in combination with in silico methods. De Vries was proud to point out that in her department they are no longer doing any nonhuman animal testing, focusing instead on stem cells and other in vitro techniques.[120] She also pointed out that more will be needed than just developing new techniques because implementing them can be very difficult. If the system of nonhuman animal testing works well for industry and regulators, they will need a good reason to change it.

5.7 CONCLUSION

The XPA-mouse project was looked back on as having brought many good things to individual researchers, RIVM departments, and the institute as a whole. You could say that not only did the humans make the mouse, the mouse also made the (careers of) humans. The XPA-mouse model was made and shown to be more sensitive to carcinogens, leading to a publication in *Nature*, which opened up opportunities for careers

116 Resnik, Ethical Issues Concerning Transgenic Animals.

117 Schuppli et al., Expanding the Three Rs.

118 Veterinaire Hoofdinspectie van de Volksgezondheid, Zo Doende 1996, Jaaroverzicht van de Sectie dierproeven (Rijswijk, 1997). Ministerie van Landbouw, Natuur en Voedselkwaliteit, 'Advies NCad Genetisch gemodificeerde dieren in voorraad gedood - Rapport - Nationaal Comité advies dierproevenbeleid', 2015 <https://www.ncadierproevenbeleid.nl/documenten/rapport/2015/11/1/ncad-advies-in-voorraad-gedood> [geraadpleegd 12 September 2018].

119 Ministerie van Landbouw, Natuur en Voedselkwaliteit, 'Advies NCad Genetisch gemodificeerde dieren in voorraad gedood - Rapport - Nationaal Comité advies dierproevenbeleid', 2015.

120 At the time of the interview, De Vries still worked at the RIVM. In 2018 she left the RIVM and became director of Science and Technology at the Dutch Forensic Institute.

and participation in the ACT project. The XPA-mice were also the reason that the RIVM became part of an NIH funded ageing project, which it has continued until today, many years after the XPA-mice were excluded from the project. Yet while creating international work for the RIVM was certainly part of the reason for participating in the ACT program, to begin with there were other reasons for developing the XPA-mouse model.

The main reason for developing the XPA-mouse model was as an alternative to the chronic bioassay in mice to test carcinogenicity. The mouse model's potential to reduce and nonhuman animal testing was what justified breeding and testing thousands of these mice. Yet the XPA-mice have not been used in regulatory carcinogenicity testing and it seems highly unlikely that they ever will be. Transgenic mice in general did not made the breakthrough in regulatory testing that was expected two decades ago. While transgenic techniques in the early days held the promise of being able to make a mouse that would respond just like a human in relevant ways, this was deemed unrealistic by the time the ACT program had ended. Transgenic mouse models turned out to have many limitations and to be more unpredictable than expected, making them valuable only in conjunction with other tests in a weight of evidence approach and only in specific circumstances. The story of the XPA and XPA/p53 mice was further complicated by issues relating to the evaluation research, costs, and marketing. While some people saw the XPA/p53 model as very promising, lack of data and high costs made this model unappealing to industry, especially compared to the p53 model that was cheaper, more extensively researched, and recommended by the ICH. Even industry that was interested in purchasing XPA or XPA/p53 mice was unable to do so, as the mice were never made available commercially.

While in Europe the use of mice and rats in carcinogenicity testing has been reduced in recent decades (especially for testing chemicals), this was not because of the XPA-mouse. Where this mouse model was used, it was for non-regulatory purposes. Yet it did not seem to be an issue that the original goal of finding an alternative carcinogenicity test was not achieved; many of the people involved said they did not know exactly what happened to the XPA-mice and what they were used for. This ties in with some broader criticisms expressed lately regarding how AECs operate. While AECs require justification for nonhuman animal experimentation prior to the performance of an experiment, the AEC does not look back to see if goals have actually been achieved. This retrospective analysis could be very insightful, especially in cases where nonhuman animal testing is done to develop an alternative to reduce animal testing, given that it has proven very difficult to validate and implement such alternatives.

Barriers to implementation, as mentioned above, are often risk aversion and regulations, two issues that were also part of this case study. The added value of the mice chronic bioassay was questioned by industry but performed in order to comply with regulations and preferred over transgenic alternatives because it was more predictable, making it less risky. The limited value of the mice chronic bioassay also raised the question of the value of transgenic mice test intended to replace it (aside from complying with regulations). While the ICH and FDA are in the process of again evaluating several transgenic mouse models, now also for the purpose of replacing the rat bioassay for pharmaceutical safety testing, the RIVM is largely moving away from transgenic animals. No more transgenic animals are bred at the animal research center and the focus for the future has shifted to humane studies and stem cell work.

CHAPTER SIX

Part Two: The Life of an XPA-Mouse: Becoming with Humans in Laboratory and Law

CHAPTER 6: PART TWO: THE LIFE OF AN XPA-MOUSE: BECOMING WITH HUMANS IN LABORATORY AND LAW

6.1 INTRODUCTION

As I argued in the introduction and in Chapter 1 of this thesis, I consider nonhuman animals to be historical actors and subjects worthy of investigation in their own right. To account for the lives of past nonhuman animals, I aim to write multispecies histories that contribute to a deconstruction of the animal-human divide. For this case study, this means not (only) looking at how XPA-mice have affected (human) history but considering the lives and experiences of mice and humans to be co-constitutive. I analyze this mouse-human co-constitution by zooming in on the daily practice of the laboratory and interspecies relationality within the lab. Drawing on theories of posthumanism, STS, and political science, I describe and analyze the 'laboratory choreography' from which the XPA lab mouse hybrid emerged.[1] To deconstruct the animal-human divide that underpins this choreography (but also gets challenged in it!), it is necessary to look not only at entanglement in the lab but also beyond at interspecies power relations and what these meant for the XPA-mice. Therefore, I will focus not only on XPA-mice becomings in the lab but also on XPA mice becomings in laws and regulations.

The chapter starts with the first act of the choreography: breeding XPA-mice (6.2). This is followed by a section on the second act: experiments with XPA-mice (6.3). In Section 6.4, I zoom out to take a closer look at socio-cultural power relations and XPA-mice becomings in the legal realm, focusing on both the micro- and macro-agency of the mice. Together, these sections will show that while there have been some opportunities for mice and humans to challenge the object status of mice and a strict animal/human dichotomy, on the whole response-abilities were severely limited and many manifestations of agency foreclosed upon. In the final, concluding section (6.5), I reflect on this finding and what this has meant for the lives of the XPA-mice at the RIVM.

6.2 ACT ONE: MICE BREEDING

In a discussion of rat-human choreographies in the laboratory, Birke et al. argue that:

> The rat itself is an agent in the process, whether it obligingly reproduces to order or squeals and bites the experimenter. So too are the technologies (cages, etc.) which produce and are produced by rats-in-laboratories. Indeed, what we understand as 'the laboratory rat' is something of a hybrid, constituted jointly by the animal, the people and various associated technologies (standard cages; devices for weighing or killing; food-stuffs and so on: see Birke and Michael, 1997). In that sense, 'laboratoryratness' is a part performed to fit very precisely into the scientific enterprise; meanings

1 These theories are described extensively in chapter 1 and will therefore not be explained as detailed in this chapter. Instead, they are employed in analyses of the empirical material.

emerge from a nexus of apparatuses, animals and people.[2]

Following this approach, we can see how out of the XPA breeding choreography, a specific type of laboratory hybrid emerged: the "breeding mouse". Alongside it emerged the "human breeding technician" and the "breeding room", all co-constituted by mice, humans, and non-living materials and technologies. Cages were a key part of this, as well as breeding technologies. Both were geared towards making the breeding process as efficient as possible.

Humans held the XPA-mice in cages to prevent them from leaving. This may seem too obvious to even mention, but let us pause for a second and consider what a cage does. A cage first of all controls the space you can and cannot be in and who you can and cannot have contact with inside the cage. Beings you share the cage with or who have access to it cannot be avoided. The location and physical characteristics of the cage determine what you can observe and who you can contact outside of the cage and vice versa. A cage is also a constant reminder of the liveliness of these mice—dead mice or non-living materials need not be confined. The picture below shows a typical layout of one of the several animal rooms at the XPA-mouse breeding facility.

Figure 6.1 Animal Breeding Room. Source: De With.

2 Lynda Birke, Mette Bryld, and Nina Lykke, 'Animal Performances', Feminist Theory, 5.2 (2004), 167–83 <https://doi.org/10.1177/1464700104045406>, 173.

Cages were stacked eight high in shelves, placed alongside the walls of the animal room. The cages are placed in such a way that the humans would have easy access to all the mice and good visibility of all the cages, so that they could do their work efficiently. With the design of the animal room created from a human efficiency perspective and the picture taken from a human vantage point, we have to make an effort to see what this means for the mice who lived in these cages. For example, we can see the mice have many neighbors who they can see, hear, smell, but not touch (except for the ones they share a cage with). In addition, the set up means that the mice cannot hide from the human gaze or escape the human hand when it comes to pick them up.

For cleaning purposes, mice were picked up and temporarily placed in a different cage regularly and then put back again into their cleaned cage. For efficiency reasons, ATs picked up a "bunch" of mice at a time, thus involving not only a touching between human and mouse, but also several mouse bodies being squeezed together.[3] Animal technician Piet de With mentioned these moments of "handling" the mice as the moment when mice were most likely to bite:

> But the lab mice here, yes I have been bitten, but that was more your own clumsiness. And if you grab one too tight or the wrong way, then it is logical that he wants to defend himself.

Not only is the mouse here recognized as active, as someone who can dislike and bite, but in addition the agentic capacity to act with a goal in mind (i.e., biting to defend) is attributed to the mouse. This biting mouse challenges her status as object and can teach the human to be more careful in handling mice in the future, as both mice and human adapt their bodily responses together. If we focus narrowly on this bodily entanglement included in the XPA-choreography, it might lead us to think of "handling" as a mouse-human "collaboration". Such a narrow focus might, however, result in us missing all the response-abilities foreclosed for the mice (e.g., leaving the laboratory).

The type and size of the cage used was determined by the interaction of: a human quest for efficiency, mice mating and maternal care behaviors, dimensions of the animal rooms and available cages, and animal welfare regulations. According to De With, the AT responsible for breeding the XPA-mice, breeding was all about achieving 'minimal stable space, maximum production per woman'.[4] As he explained, breeding efficiency was measured using the Production Efficiency Index (PEI), defined as average offspring per female per week. A mouse line with a PEI of 1.9 was considered a well breeding line. This PEI is influenced by mice behavior such as maternal care (i.e., better maternal care means more surviving babies), which is in turn influenced by cage size.

In the picture below, four types of cages are shown, from top to bottom: type 1-elongated, type 2, type 3, and type 4.

In a breeding efficiency study conducted by De With, it was found that mice PEI is higher in cage type 2, where the mice have more space than in type 1-elongated.[5] Yet

3 Interview De With.

4 This quote is from a PowerPoint presentation De With used when giving a presentation to colleagues on breeding mice, which he showed me during the interview. The Dutch term vrouw is translated as woman here, as that is the most common translation. It could also be translated as 'female', but nonhuman females are generally referred to as vrouwtje in Dutch.

5 Interview De With and PowerPoint presentation on the study by De With.

Figure 6.2 Four types of cages. Source: De With.

Figure 6.3 A mouse family in a cage. Source: De With.

because type 1-elongated is narrower than type 2, it is possible to fit more type 1-elongated than type 2 cages into the same animal room. As a result, XPA-mice lived in type 1-elongated cages during the breeding process. The regular type 1 cages could not be used because they were deemed to be too small by animal welfare regulations. Regulations also stipulated that the cages be 'enriched' with bedding and nesting material. According to De With, not all lines of mice did something with the nesting material, but

XPA-mice created a 'nice little nest'.[6] The enrichment of cages was seen as beneficial for both mice and the experiment, as less stressed mice made better research instruments. The ATs searched for a type of enrichment that suited a specific strain of mice.[7] In doing so, they went beyond what was stipulated in welfare regulations, something that is commonly found in studies of AT's and experimental animals.[8]

The 'breeding system' also focused on efficiency. A male and female mouse lived together 24/7 in the same cage; a system called permanent meeting breeding. When a female mouse gave birth, the baby mice stayed in the same cage for about eighteen to twenty days. The picture above shows one such mouse family together in a type 1-elongated cage. The permanent meeting system had the "advantage" of making use of the female mouse's postpartum estrus. After giving birth, she is fertile for 12–24 hours. If the male mouse is in the same cage the whole time, the female mouse can become pregnant again immediately after giving birth. As implantation is slightly delayed in nursing mice, the next litter is usually born after 21–22 days, just after the previous litter has been weaned. Thus, if all went according to human plans, female mice were pregnant almost constantly. A female mouse was put in a breeding cage with a male mouse at about ten weeks of age. After six months or so, they started to "produce" less babies and humans would subsequently kill them. The male mice could be used for 'two rounds' of breeding and because the XPA was an inbred mouse line and the male mice could thus be paired with their own daughters.[9]

The XPA breeding choreography as described so far involved many intimate mouse-mouse interactions: intercourse, giving birth, nursing babies, siblings huddling together (as can be seen in Figure 6.3), etc. Here, we can catch a glimpse of other becomings of these mice: partners, mothers and fathers, and warm bodies to lie against. This reminds us that these mice create their own meaning in relation to one another. For the mice to become research materials, intra-actions with humans and technologies are required; it is not something they *are* in some essential way, hence the hybrid Birke et al. speak of.[10] It also requires a socio-cultural context in which mice are "breedable" and "killable", a context which forecloses on many possible worlds for the XPA-mice that were bred to be research animals.

Of all the XPA-mice born in the breeding facility, only the ones with genotype -/- were used in experiments. Genotyping to find the desired mice was conducted by cutting a piece of each mouse's tail, which was sent to the lab for determination. For identification purposes, cuts were also made in the ear(s) of mice (see Figure 6.4). For example, mouse five has one ear clip in the left ear and two in the right. This was not a stand-

6 Interview De With.

7 Interview De With.

8 Carrie Friese and Joanna Latimer, 'Entanglements in Health and Well-Being: Working with Model Organisms in Biomedicine and Bioscience', Medical Anthropology Quarterly, 33.1 (2019), 120–37 <https://doi.org/10.1111/maq.12489>; Beth Greenhough and Emma Roe, 'Exploring the Role of Animal Technologists in Implementing the 3Rs: An Ethnographic Investigation of the UK University Sector', Science, Technology, & Human Values, 43.4 (2018), 694–722 <https://doi.org/10.1177/0162243917718066>; Robert G. W. Kirk, 'Recovering The Principles of Humane Experimental Technique: The 3Rs and the Human Essence of Animal Research', Science, Technology, & Human Values, 43.4 (2018), 622–48 <https://doi.org/10.1177/0162243917726579>.

9 Interview De With.

10 Birke et al., Animal Performances.

ardized system, but dependent on the AT who made the cuts. Once the mice had been genotyped, the ones with the "right" genotypes were ready to be sent off for use in experiments. The other mice were killed.

Figure 6.4 A mouse with ear cuts. Source: RIVM.

Conny van Oostrom witnessed many of these genotyping procedures and recalls the age of the mice making a lot of difference:

> If you do it quickly and at a young age, very little blood is involved. But if the animals are too old, then it does get bloody, they will have a drop of blood and then you let them go and they will go through the whole cage and touch all the walls and the whole cage will be red, that is really gross and they will need a new cage as well. But it closes rather quickly, or they squeeze it close or push it in the sawdust to close it.[11]

A mouse's ear-cutting experience depended on the number of ear cuts received and on the skill of the AT:

> Some would go cut cut, cut, cut and in no time they would have three cuts in one ear, while others tried it as well and the mouse would have no ear left in a manner of speaking. It was just really difficult, and they would prefer not to give three cuts in one ear.[12]

11 Interview Van Oostrom.

12 Ibidem.

Annemieke de Vries compared ear cuts to toe clips (which was not practiced at the RIVM, but common practice in other labs). When asked whether ear cuts were less painful, she found it difficult to judge the amount of suffering involved for the mice:

> I am not sure, you see, if you cut, the little mouth opening and a squeak, although difficult to hear in the isolator. I also worked in an animal room without isolator and then you hear them squeak, but that can also be stress from being picked up. It is always difficult to say, they must feel something, that is for sure. Yes, the ear cut was also not nice, because they did that with the same scissors [as the tail], so it would be one cut and a second and a little corner would be cut out. There were also people who preferred a tong, like a perforator for belts, but many times smaller of course. People tried to cut at the edge of the mouse ear and then it would be done with one cut. People had their preferences.

These narratives point towards the situatedness of the experiences of care and suffering; even within one laboratory individual experiences of the common practice of tailing and ear clipping can vary greatly, depending on the mice-human duo involved. Not only the age of the mouse, but also the bodily adaptation of the human to the practice of ear clipping affected mouse suffering. The older mice who bled as a result of the tailing responded by running frantically through the cage, against the walls. While this behavior likely did little to alleviate the suffering, it does indicate to attentive humans that the tailing is painful, thereby challenging the mouse's object status and bringing attention to their liveliness instead. The human can respond by learning to execute these movements less painfully, or by asking someone more skilled to perform them. Responses that are excluded from the breeding choreography are those that involve not tailing the mice. Not only would this go against protocol, it would also simply not be conceived of as an option; sacrificing the experiment rather than the mice would go against social-cultural power relations. Genotyping was a determining moment for mice because their (reduction to) genotype and human valuation thereof decided their fate as either "mouse killed in stock" or part of the "lab mouse" hybrid.

6.3 ACT TWO: THE EXPERIMENTS

After the first XPA-mice were created, experiments were conducted to test their increased sensitivity to carcinogens. As described in the previous chapter, in 1996, XPA-mice became part of the international Alternatives for Carcinogenicity Testing (ACT) program.[13] In this program, which sought an alternative for the chronic mouse bioassay, twenty-one substances were tested on five TG-mouse models, a neonatal mouse model, and an in vitro Syrian hamster embryo assay. At the RIVM, the experimental choreography started with mice moving away from their parents and from the breeding facility to the experimental facility.[14] Scientists ordered mice from the breeding facility who

13 ACT was initiated and coordinated by the International Life Science Institute (ILSI) and the Health and Environmental Science Institute (HESI) in the US, in collaboration with the Central Institute for Experimental Animals (CIEA) in Japan and a European working group led by the RIVM.

14 I focus on the carcinogenicity experiments that these XPA-mice were part of. They have also been used in

would arrive in boxes at the experiment's location. There they were separated from their siblings when assigned randomly to experimental and control groups.[15] Male and female mice lived separately from one another, meaning that mating, pregnancy, and babies were not in their future. While according to respondents, duo or group housing was always preferred, archives show that mice were also housed individually in some experiments. For example, in a six-month oral carcinogenicity study with Cyclosporin A, 342 mice were housed individually.[16] The responses to the new living arrangements varied between mice. Female mice generally had no problem living together in one cage, but male mice sharing a cage could sometimes become aggressive towards one another. Humans responded to this aggression by separating the mice. The aggressive mouse behavior affected not only their own living situation but in certain experiments also affected the study in ways which were relevant to humans. Aggressive mouse behavior could make it more difficult to determine research results in skin cancer studies, as it was not always clear if skin damage was the result of mice fighting or of the experiment.[17] Because of this male-on-male aggression, in some studies females were housed together whilst males lived individually from the start. The behavior of some male mice, in that way, also affected the living situation of future mice, who were not given the opportunity to be aggressive towards a cage mate anymore.

During the carcinogenicity experiments, mouse-human intra-action consisted mostly of handling the mice to clean the cages and exposing mice to test substances. XPA-mice were exposed to either carcinogens or non-carcinogens during either six or nine months.[18] Exposure happened in several ways: UV-light exposure (Figure 6.5), rubbing a substance on the skin, force feeding (gavage), or mixing a substance in the food.

The mice that were part of the skin exposure studies were shaved on a weekly basis. All the mice were checked regularly for tumors or other signs of illness. After the exposure period, the mice were taken to the pathologist to be killed and their tissues were analyzed.

During the experiments, suffering was caused by the treatment received (compound exposure), the effects of the treatment, and illness unrelated to the experiment. Gavage exposure was mentioned by most of the respondents when the issue of suffering was brought up. With gavage feeding, mice have a tube inserted into their stomachs via their mouths through which they are force fed a compound dissolved in oil. It was obvious to the respondents that the mice did not like the gavage feedings, some making comparisons to how it would be for humans: 'And especially the gavage they did not like, you as a human are also not like some kind of goose […]'[19] and in response to the question 'Do you think gavage entails suffering?', 'Yes, if I grab you and get a big syringe and fill

other types of experiments, mainly basic research about ageing.

15 Interviews De Vries and Van Benthem.

16 Six-month oral carcinogenicity study with Cyclosporin A in XPA -/- mice by R. Beems, 2 June 1998. RIVM Archive, file no. 650080/9800518.

17 Interview De Vries.

18 The experiments on XPA-mice involved exposing them to a variety of compounds: UVB, DMBA, B[a]P, Cyclosporin A, Phenacetin, Resperine, D-mannitol, PhIP, p-cresidine, 2-AAF. Coen F. van Kreijl and others, 'Xpa and Xpa/P53 +/- Knockout Mice: Overview of Available Data', Toxicologic Pathology, 29.5 (2001), 117–27 <https://doi.org/10.1080/019262301753178528>.

19 Interview De Vries.

Figure 6.5 Mice being exposed to UVB. Source: RIVM.

your stomach with stuff, you do not enjoy it, not even if I sedate you'.[20] Van Oostrom also noticed how mice adapted their responses to the gavage feeding over time:

> Gavage studies, that was in the early days, they also did not like that. But they would get used to that. That is also what the caretakers would say, it was in a manner of saying like, 'well let's do this' with their mouth already open and, well shove it in and get it over with. Of course, it was not really like that, but they got used to it and accepted it, got easier over time.

In later studies gavage feeding was often replaced by exposure through food, which was seen as not causing any suffering, apart from sometimes the mice not liking the taste of the food too much.[21] While it was sometimes unclear what "suffering" meant for a mouse, in certain situation it was obvious to the humans in observation that the mice were experiencing pain. One treatment that caused a noticeable reaction of suffering was exposure by injection and especially intraperitoneal (IP) *injections:*

> Suffering? Yes well, the injections of course, we have also done IP injections, they are supposedly not nice. You can also see that by the animal's behavior: they would huddle in a corner for a while, you would really notice that.[22]

The first exposure studies conducted with the XPA-mice were done with UV-B and DMBA. Although the exposure itself was not mentioned to be painful, these compounds had more acute effects than other exposure routes, causing not only tumors but also irritation of the skin. Such reactions were looked for during clinical inspection of the mice and written down on a check-in list. In the DMBA check-in list from September 1994, one of the entries reads: 'inflammation, tumor front leg, bad condition, red skin,

20 Interview Van Benthem.

21 Interviews Van Benthem, Van Oostrom, De Vries.

22 Interview Van Oostrom.

and scabs'.[23] In the same month, an interim section and histopathology of the killed mice were performed because of a severe skin reaction after two exposures to DMBA.[24]

Sometimes, effects of exposure were unexpected. In the first study with PhiP, XPA-mice who received the highest doses were in such a bad condition after a few weeks that they either died or were so ill that they had to be removed from the experiment.[25] The study was then redesigned with lower doses.

The development of tumors was another type of suffering obvious to the respondents: 'When a mouse gets a tumor, that bothers him of course'.[26] Here certain behavior in the mice was also seen to be a sign of suffering: 'And sometimes it was really sad, then they would have a big tumor and crawl away into a corner, that is what you see'.[27] When it came to tumors, measures were taken to make sure the mice did not suffer more than was necessary for the experiment:

> And you know skin cancer you see and then we would have the vet there and beyond a certain set tumor size, they would get euthanized. With other tumors, you do not see it, there was a lot of control, I remember they would check the skin of the neck, if it would stay up, then we would euthanize. We were not in it for very ill animals, not relevant.[28]

The success of practicing humane endpoints was seen to depend on the human's ability to read a mouse's health status: "[...] weak, ill animals were put down, the pathologist I worked with, he could read and write with those animals and A1 was also on top of it [...]."[29]

Care practices such as cage enrichment and humane endpoints required bodily attunement between human bodies and mouse bodies, emphasizing how both mice and human bodies are co-constituted in this multispecies choreography.[30] Several non-AT respondents mentioned how ATs really cared about the animals and took good care of them. Attention to welfare and acts of care, even if not (just) instrumental in conducting the experiments, in this way also helped to facilitate experimental practices because it helped to make experimentation acceptable as 'good science'.[31]

Ethnographic research by Arluke has shown that within the lab space, nonhuman animals are not continuously objectified but rather move back and forth between being pet and object through processes of anthropomorphizing and counter-anthropomorphizing.[32] This can be seen as a way in which humans deal with the psychological de-

23 Check-in lijst klinische bewaking, September 1994, RIVM Archive, file no. 4885.

24 Dr. P.W. Wester, Uitslag histopathologie interimsectie (1994), RIVM Archive, file no. 4885.

25 R.B. Beems, Carcinogenicity of PhIP in XPA -/- mice: korte rapportage pathologie, 26 March 1998, RIVM Archive, file no. 199600363.

26 Interview Van Benthem.

27 Interview Van Oostrom.

28 Interview De Vries.

29 Interview Van Steeg.

30 For more on the role of attunement in the relation between ATs and experimental animals see: Greenhough and Roe, Attuning to Laboratory Animals.

31 Druglitrø, Skilled Care.

32 Arnold B. Arluke, 'Sacrificial Symbolism in Animal Experimentation: Object or Pet?', Anthrozoös, 2.2 (1988), 98–117 <https://doi.org/10.2752/089279389787058091>.

mands of the job. While objectification makes killing (or "sacrificing") the lab animals easier, anthropomorphizing is a way for humans to deal with the empathy they feel for the lab animals. According to Arluke, objectification is facilitated by de-individualization, hence the common practice of giving lab animals numbers instead of names. This de-individualization occurs more easily in "lower" animals that are handled in large "batches" instead of individually. Animals that spend a long time in the lab are more likely to be named and names are most likely to be used by those who spend substantial time with conscious animals, often ATs and caretakers. In Chapter 3, we saw that this de-individualization was relatively difficult in the case of monkeys as they were considered "higher" animals, spent a long time at the RIVM, were handled individually, and were sometimes even hand reared. The situation of the XPA mice was rather different. Humans working with the XPA-mice showed a tendency to reduce mice to groups and think of them in strains rather than as individuals:

> Grabbing each mouse individually is too much, so you grab them in a bunch [...] and with rabbits it starts that you recognize animals. A mouse is here half a year and part of a mass, you do not have them in your hands individually. Never noticed a mouse individually, the population is too big.[33]

Here we see a reference to the number of mice, time spent at the laboratory, and the handling of batches rather than as individual mice, all of which are circumstances that facilitate objectification of mice. However, De With also stressed that there was a lot of variation within the mice species. It is not individual variation he is referring to, but differences between strains of mice. When speaking about what would be typical of the XPA strain he said:

> The XPA line, Black 6, homozygous, responded differently from the wild type. They were unrulier and would jump out of the cage. A normal Black 6 would walk around, but you can leave the lid off when cleaning. With XPA you had to be careful and would bite uncontrolled, not when you are clumsy, but just when you stick your hand in. Has to be the genetic alteration, because wild type did not have it.[34]

While XPA-mice were relatively easy to de-individualize, but also in their situation, some tension between seeing the mice as materials and as fellow living beings was present. This tension is something Van Oostrom was aware of and reflected on in her interview:

> After a while, you start hoping for tumors, hoping for them to get symptoms quickly. But then you also realize that you are thinking about a living being that you are sacrificing. We were aware of that.[35]

She also described how one of the pathologists dealt with this tension by thanking a

33 Interview De With.

34 Interview De With.

35 Interview Van Oostrom.

mouse he had just sacrificed in the name of science. Of course, using terminology such as sacrificing and "removing" instead of killing also serves to ease the tension.

These narratives of care and suffering bring various forms of suffering, response-abilities, and attributions of agency to our attention, all functioning as micro-challenges to the object status of nonhuman animals and animal/human dichotomy.[36] The mice's opportunities to mitigate or avoid suffering altogether were meanwhile virtually non-existent. One instance that could be seen as such would be that of a mouse "learning" that gavage feeding is less unpleasant when being cooperative. Considering the human/mouse entanglement in gavage feeding here we must again be mindful of what is excluded for these mice (from not being gavage fed to not being part of any experiment at all). In most cases, the only responses available were those that expressed but did not alleviate suffering (e.g., biting, huddling in a corner). The refinement measures taken by humans and their responses to mouse suffering were limited as well, given that the best possible response to a sick mouse was killing and thanking her and the best possible response to a mouse trapped in a cage was giving her some sawdust.

Acts of care were certainly an important part of XPA-mice and RIVM human relations. Overall, however, the 'laboratory-ness' and object status remained very stable as it was continuously reproduced in every act of tailing, ear clipping, caging, exposing, handling, and finally killing (acts that were maybe done *with* care, but not *out of* care). As Birke et al. and Hollins et al. emphasize, this iterative congealing process is important.[37] It is where emerging worlds become relatively stable and the exclusion of other becomings become difficult to reverse. These daily laboratory doings also intra-act with sociocultural power relations and legal practices, however, which are considered next.

6.4 XPA-MICE BECOMINGS IN THE LAW

In this section, I first look at how legal practices and species power relations in general intra-acted with the laboratory choreography to constrain possibilities for XPA-mouse micro-agency. I then analyze mouse agency on the macro-level: were they able to affect the legal and political dimensions of their lives?

6.4.1 Micro-agency

In the Netherlands, the first law on animal testing was accepted in 1977 and enacted in 1980. This law stated that animal testing was only allowed when no non-animal test was available and when the interest of the test outweighed the suffering of the tested animals. "Animals" in this legal context means 'nonhuman vertebrates and cephalopods'.[38]

36 According to Irvine, play between human and nonhuman animals can be seen as micro-challenges to a human/animal dichotomy as play '[...] honors animals' subjectivity and communication skills, making this everyday activity an act of individualized resistance to human disregard for non-human life'. Leslie Irvine, 'The Power of Play', Anthrozoös, 14.3 (2001), 151–60 <https://doi.org/10.2752/089279301786999454>, 1. In a similar vein, mice biting humans when they do not want to be held can also be seen as such a micro-challenge in which mice try to resist human domination over their lives, asserting themselves as subjects rather than objects.

37 Birke et al., Animal Performances; Gregory Hollin and others, '(Dis)Entangling Barad: Materialisms and Ethics', Social Studies of Science, 47.6 (2017), 918–41 <https://doi.org/10.1177/0306312717728344>.

38 Overheid.nl, http://wetten.overheid.nl/BWBR0003081/2018-01-13 (visited 10 September 2018). See Chapters 2 and 4 for an elaborate discussion of nonhuman animal testing law, policy and societal perspectives.

As in other European countries, the 3Rs were the dominant framework for looking at animal testing in the Netherlands in the 1990s when the XPA-mouse experiments were being conducted.[39] In 1996, permission from an Animal Experiments Committee (AEC) became obligatory. In the AEC applications written for the experiments with the XPA-mice, the 3Rs discourse is clearly visible.[40] Respondents also referred to the 3Rs:

> We always had the same justification for the experiment, you want a test that is bearable for those animals, because it is shorter, also it is cheaper. In the normal test, you would have two species and fifty animals per sex and dose, 800 in total if you succeed right away and it takes two years. We only used fifteen [per group], huge reduction, it is both reduction and refinement.[41]

Both Dutch animal testing law and AEC applications seemed to recognize the aliveness of (certain) nonhuman animals in general and of XPA-mice in particular by recognizing their ability to suffer and even designing experiments to reduce nonhuman animal use and suffering. At the same time, the object status of nonhuman animals remained stable. Even if reducing animal suffering was an important motivation for these experiments, the use of nonhumans (but not humans) for human benefit when deemed necessary (by humans) was not questioned. At the level of the law, nonhuman animals legally were and still are property like cars and cages; only humans are legal subjects.[42]

Practices of making and enacting laws that separate humans and nonhumans as subjects and object do not reflect a pre-existing human-subject and nonhuman-object but rather produce and reproduce this boundary, which in turn has consequences for which worlds can and cannot emerge. While the 3Rs and experimental legislation prohibited certain experiments, which were seen as unethical, they legitimized others at the same time (such as those conducted with the XPA-mice) by deeming them "ethical". Analyzing this legal practice as a boundary making practice, we can see how each enactment of the law and the 3Rs reproduced an animal-object/human-subject boundary which had consequences for the XPA-mice worlds which could emerge. There was no questioning of the human/animal dichotomy that makes (only) nonhuman animals "testable" and "killable" in the first place. Considering the consequences of this for XPA-mice response-abilities, we can say that within such an anthropocentric regulatory framework and considering interspecies power relations in general, micro-level manifestation of agency were very limited.[43] Consequently, there was little space within the XPA-mouse chore-

39 M. C. Pijnappel, Lost in Technification : Uncovering the Latent Clash of Societal Values in Dutch Public Policy Discourse on Animal-Testing Alternatives ([S.l. : s.n.], 2016); M. J. W. A. Schiffelers, 'Animal Testing, 3R Models and Regulatory Acceptance : Technology Transition in a Risk-Averse Context', 2016. See also Chapter 2.

40 Carcinogeniteit Cresidine en AAF in XPA muis. Proefopzet 199800744, 17/12/1998, p.164, RIVM Archive, file no. 24748.

41 Interview Van Benthem.

42 Cf. Eva Meijer, 'Interspecies Democracies', in Animal Ethics in the Age of Humans: Blurring Boundaries in Human-Animal Relationships, ed. by Bernice Bovenkerk and Jozef Keulartz, The International Library of Environmental, Agricultural and Food Ethics (Cham: Springer International Publishing, 2016), pp. 53–72 <https://doi.org/10.1007/978-3-319-44206-8_4>.

43 By interspecies power relations in general, I refer to the omnipresence of human exceptionalism in popular thinking. Jozef Keulartz and Bernice Bovenkerk, 'Changing Relationships with Non-Human Animals in the Anthropocene—An Introduction', in Animal Ethics in the Age of Humans: Blurring Boundaries in Human-Animal Rela-

ography for anything else to emerge than the "XPA-lab mouse" hybrid.

6.4.2 Macro-agency

It will probably come as no surprise to you that no XPA-mice were consulted in the process of approving the experiments on them. Certainly, there was some concern for their suffering and an assumption that they would have preferred not to be experimented on, but the decisions making them "breedable" and "killable" were seen as decisions for only humans to make. They were in other words not recognized as *political agents* or as living beings with the potential for macro-agency, the ability to make decisions regarding the larger dimensions of their lives. The relation between humans and XPA-mice in the legal realm was of course not exceptional. Representation of nonhuman animals in general was and still is weak and only on human terms and, as we saw in Chapter 2, nonhuman animals continue to be silenced politically.[44] Where the response-abilities of the XPA-mice were severely limited on the micro-level, they were completely absent on the macro-level.

6.5 CONCLUSION

In this chapter I looked at the becomings of mice in the laboratory and in the legal realm. The laboratory choreographies of breeding and experimentation showed a large discrepancy between what is written in standardized protocols and articles and the daily relations of mice, humans, and technologies in the laboratory. Rather than mice being "just materials", as they are often depicted in protocols, we saw mice and humans interacting as embodied individuals, responding to each other as living beings and thereby affecting experimental practices. Care and attunement formed an integral part of mouse-human relations and were more than just "instrumental tools" in scientific knowledge production. Mouse suffering was recognized and responded to with refinement measures such as humane endpoints. At the same time, response-abilities of both mice and humans were very much limited and mice also became research materials, a tension that humans were well aware of. This making "mice into materials" was legitimized both legally through regulations and AEC procedures and through psychological mechanisms. Taking a closer look at the law showed us that the anthropocentrism of legislation constrained the micro-level response-abilities. There was space for some minor challenges to their objectification, but, overall, their ability to affect their day-to-day life was very limited. As I have pointed out in several of the previous chapters, the anthropocentrism of the decision-making process regarding the permissibility of nonhuman animal experimentation has remained unchallenged. XPA-mice and other nonhuman animals have not been recognized as political actors who could potentially participate in democratic decision-making processes. For XPA-mice, this has meant a foreclosure of potential opportunities to affect larger dimensions of their lives.

tionships, ed. by Bernice Bovenkerk and Jozef Keulartz, The International Library of Environmental, Agricultural and Food Ethics (Cham: Springer International Publishing, 2016), pp. 1–22 <https://doi.org/10.1007/978-3-319-44206-8_1>; Jeffrey Moussaieff Masson and Susan McCarthy, 'Unfeeling Brutes', in Animal Ethics in the Age of Humans: Blurring Boundaries in Human-Animal Relationships, ed. by Bernice Bovenkerk and Jozef Keulartz, The International Library of Environmental, Agricultural and Food Ethics (Cham: Springer International Publishing, 2016), pp. 103–18 <https://doi.org/10.1007/978-3-319-44206-8_7>.

44 Will Kymlicka, '[Review] Robert Garner and Siobhan O'Sullivan (Eds). The Political Turn in Animal Ethics. Rowman and Littlefield, 2016.', Animal Studies Journal, 6.1 (2017), 175–81; Meijer, Interspecies Democracies.

CONCLUSION

CONCLUSION

On January 24, 2021 Dutch scientists Willem Mulder and Judith Homberg published an opinion article about nonhuman animal experimentation in the newspaper *De Volkskrant*.[1] In this article, which was signed by one hundred scientists, they stated that animal-free research was both undesirable and impossible. The COVID-19 pandemic was used as a "hook" to argue for the need for nonhuman animal testing both now and in the future, suggesting that a vaccine would never have been developed as quickly as it was without nonhuman animal experimentation. According to the authors, the present ambition of the Dutch government to be a "frontrunner" in animal-free innovation was therefore a bad idea: 'We emphasize that replacing animal experimentation is very far from being achievable and that plans for an accelerated transition towards using as much lab animal-free research as possible are very unwise'.[2] According to the authors, such plans would not only have consequences for public health but also for Dutch science: 'We are chasing biomedical research and the biotech industry away from the Netherlands'.[3] The authors were not only critical of the government for being persuaded too much by arguments of animal ethics but also of some organisations where research is being conducted:

> Because a lobby of politicians and NGOs is being facilitated by government organisations such as the RIVM and some university administrators, the impression is created that we can use alternatives for animal experimentation in the near future. This is wrong [...].[4]

Other scientists were quick to respond with an alternative reading of the pandemic and government policy. In an opinion article which was also published in *De Volkskrant*, Merel Ritskes-Hoitinga argued that COVID-19 was reason to again ask the question of why we are still doing so many nonhuman animal experiments when they are often run concurrently with human trials and are often outperformed by nonanimal methods? 'We do animal tests because we are used to it and because the law often requires this, but we are playing catch-up'.[5] The government ambition of being frontrunner in animal free innovation is not detrimental to public health or science, but 'will lead to better science and a better world for human and animal'.[6]

The arguments in this recent debate should sound familiar; we have seen them pop up throughout this thesis and some have been recurring since discussions about non-

1 Willem Mulder and Judith Homberg, 'Opinie: Zonder proefdieren hadden we nu geen vaccin tegen het coronavirus', de Volkskrant, 2021 <https://www.volkskrant.nl/gs-bc8e13c7>.

2 Ibidem.

3 Lydia van Aert, 'We kunnen nog niet zonder proefdieren', 2021 <https://www.cursor.tue.nl/nieuws/2021/januari/week-4/we-kunnen-nog-niet-zonder-proefdieren/>.

4 Ibidem.

5 Merel Ritskes-Hoitinga, 'Opinie: Proefdiervrije alternatieven leiden tot betere wetenschap', de Volkskrant, 2021 <https://www.volkskrant.nl/gs-b9def180>.

6 Ibidem.

human animal testing legislation first started in the 1880s. We have also seen that there has been consensus among scientists and government for quite some time about the fact that science would ideally no longer be using nonhuman animals in experiments. The aim of reducing and eventually replacing nonhuman animals with alternatives has been on the policy agenda since the 1980s. We have seen, however, that "solving" the "wicked problem" of how to make the transition towards nonanimal alternatives has proven more difficult than it was initially thought to be.

This thesis began with the question: 'How did practices of nonhuman animal experimentation and its alternatives develop in the Netherlands, and at the RIVM in particular, in the period between 1950–2020?' This question was further specified by asking what these developments have meant for the experiences of various nonhuman animals across different time periods. Over the course of both case studies and a more general overview—combining the micro- and the macro-levels—I answered these questions. In this conclusion, I first consider the insights that this thesis has brought forward about the history of nonhuman animal testing and alternatives in the Netherlands. I then reflect on the aim of writing multispecies histories and discuss what insights from multispecies histories could mean for future directions of research. Could they perhaps inspire a new way of looking at the transition away from nonhuman animal testing?

HISTORICAL INSIGHTS

A very general answer to the central question of my thesis was already given in Chapter 2, where I looked at how nonhuman animal experimentation and alternatives have developed over time in the realms of law, Laboratory Animal Sciences, society, and politics in the Netherlands between 1950–2020. I sketched broad trends, such as the popularisation of the 3Rs discourse, resistance against regulations to nonhuman animal experimentation followed by their acceptance, "ethics" entering the discourse in the 1980s and moving into the background again in recent years, and the framing of alternatives to nonhuman animal testing as a 'win-win'. We also saw how many factors other than deliberate policy affected nonhuman animal experimentation practices; for the RIVM, a change in roles played an important part in the end of nonhuman animal experimentation for the institute. Overall, the conclusion was that a great deal has changed since the 1950s, but on a more fundamental level much has also remained the same, including the omnipresence of anthropocentrism in society, as well as rhetoric and viewpoints within law, Laboratory Animal Science, and politics. What these changes and continuities meant for the lives of tested nonhuman animals varied greatly from individual to individual. On the micro-level, there was more attention for their care and welfare. The development of alternatives meant for some nonhuman animals that they were no longer used (or not brought into existence at all), for others that they were used as "replacements" for "higher" animals. On the macro-level, interspecies power relations remained stable and continued to legitimize the practice of animal experimentation.

In Chapter 3, we saw how a specific group of nonhuman animals was affected by the developments described above: the 'Polio-Monkeys'. In the 1960s and 1970s, the use of and care for the Polio-monkeys changed mostly for reasons of economics and public health. Monkeys were scarce, expensive, and sensitive to becoming ill due to stress and infections. The RIVM therefore developed new ways to produce the polio vaccine

that reduced the need for monkeys. They also implemented hygiene measure to make sure that monkeys were 'clean'. In the 1980s, we saw how "ethics" entered the scene and promoting the welfare of the monkeys came to be seen as a moral duty. Monkeys were no longer taken from the wild but home-bred at the RIVM. For the home-bred generations of monkeys, many aspects of their lives were controlled by humans, including intimate management of their reproduction. This close contact between human and nonhuman primates, as well as the fact that humans find it easy to identify with other primates, posed some challenges to the objectification of these tested animals. Likewise, compared to the use of non-primate animals, the use of nonhuman primates was questioned more strongly within society in general. Activists strategically used the hierarchy of nonhuman species by targeting the use of favoured species (primates, but also cats and dogs) in their campaigns. Eventually, the Polio-monkeys were completely replaced by the Vero cell line. Risk aversion played a big role in delaying the switch to the cell line for many years, and an infection among the monkeys, rather than ethical motives, gave the final push to making the switch. Rats are, however, still used for potency testing of the polio vaccine.

Although the use of monkeys ended completely, the continuities pointed out in Chapter 2 can be seen here as well. Nonhuman primates remained objects in a legal sense and the decision to end their use in this case was a completely human decision. The decision was made not by researchers themselves but by the AEC that had been pressuring researchers for many years to switch to the Vero cell line. Once the switch had been made for a large part of the production, the AEC did not grant permission for another year of using the monkeys just for the purposed of exporting the vaccine to countries that had not yet licensed the Vero-based polio vaccine.

An AEC rejecting an experiment was rare, as we saw in Chapter 4 in the discussion of the creation of AECs in the Netherlands. In the 1980s, not coincidentally when 'ethics' became part of the discourse on nonhuman animal testing, society and politicians demanded more accountability regarding nonhuman animal experiments. Leaving all decisions of permissibility to scientists only was no longer deemed acceptable and the government decided to create legislation making AECs and ethical reviews mandatory. This caused great concern among scientists, who fought to make the law as unintrusive as possible and to keep all decision-making power internal. Activists on the other hand strove for more openness and outsider involvement. The result was a compromise, but AECs remained a largely internal affair. Over the years, the committees became an accepted part of scientific practice and took on a legitimizing function: an approved experiment must be a "good" experiment, where good had both ethical and scientific connotations. We saw, however, that ethical reviews were problematic due to unclear and contradictory guidelines and a tendency to review scientific quality and 3Rs application rather than considering the intrinsic value of nonhuman animals in experiments and what this means for the permissibility of these experiments. As a consequence, the effects of AECs on the lives of nonhuman tested animals were largely through adjustments to experiments (such as adding the use of pain medication). On a larger scale, AECs consolidated the subordinate position of nonhuman animals.

The legitimizing function of the 3Rs and the AEC was also part of the story of the XPA-mice, whose creation and use were justified with reference to the 3Rs. In their two-part story, we saw that even though the XPA-mice were in the end not used as intended, they still had great value for humans and the RIVM by creating further research oppor-

tunities. Chapter 5 showed the variety of reasons beyond the technoscientific aspects that the XPA-mice were not used as replacements for "regular" mice in carcinogenicity testing (such as patents and costs). This chapter also raised the more general issue of TG animals, which did not live up to the promise of making mice which were just like humans in all relevant ways but did lead to many nonhuman animals being killed in stock. Additionally, the case study pointed towards risk aversion and regulations as barriers to reducing nonhuman animal experimentation.

In Chapter 6, we looked at what it was like for XPA-mice to "become with" humans in laboratory and law. In this part of the story, I paid particular attention to mouse response-abilities and the foreclosure of these in both lab and law by looking at the "laboratory choreographies" of breeding and experimentation. We saw that, like monkeys, mice were more than just materials to humans (and obviously to each other and themselves). Interspecies care and attunement formed an integral part of the lab choreography and were more than just instrumental tools in scientific knowledge production. Yet we also saw how power relations largely foreclosed on the manifestation of agency for mice and humans in the lab setting. There was space for some minor challenges to their objectification, but overall XPA-mice's abilities to affect their own day-to-day life were very small. Humans legitimized the objectification of mice both legally through regulations and AEC procedures (the "stamp of good science" mentioned before) and through psychological coping mechanisms. A closer look at the workings of the law showed that the anthropocentrism of legislation constrained the micro-level response-abilities and completely foreclosed on those at the macro-level, since XPA-mice were not recognized as political actors who could potentially participate in democratic decision-making processes.

After this reiteration of the most prominent conclusions from the separate chapters, we can now return to the main questions posed in the introduction and see if some overarching conclusions can be drawn. There are three observations emerging from the chapters taken together that I will discuss here. They concern: 1) continuity v. discontinuity, 2) the macro v. the micro: differences between species and individuals, 3) the transition from nonhuman animal experimentation to alternatives.

Over the course of this project, many people told me that 'so much has changed' in nonhuman animal testing and that we should not judge past nonhuman animal experimentation practices from our present-day perspective, since the context was so different. Indeed, the chapters have shown several major developments in practices of nonhuman animal experimentation and alternatives. From the 1950s onwards, care and welfare became integral parts of nonhuman animal testing, and in the 1980s the 3Rs became the dominant discourse and continue to be so to this day. Developing "alternatives" became a policy focus and "ethics" entered the discourse on nonhuman animal experimentation, embodied by the AECs that were tasked with ethical reviews of all experiments on nonhuman animals. These developments changed nonhuman animal experimentation practices in significant ways and as such affected many nonhuman lives. At the same time, the developments also all contributed to upholding the legitimacy of nonhuman animal experimentation, making it possible to continue with these practices by satisfying demands from society and politics for more accountability and "ethics". Strikingly, the adjustments made managed to satisfy these demands despite the fact that ethical decision making in the legislative process and in AECs was based on a mixture of incompatible ethical perspectives (e.g., utilitarianism and deontology) and was often reduced to questions of scientific quality.

Although some key changes have been identified, this thesis has also shown that there have been fundamental continuities in nonhuman animal experimentation and interspecies relations in general throughout the time period. I call these "continuities" not in order to essentialize them but to emphasize how they are iteratively reproduced to be made relatively stable (leaving space for occasional challenges). Throughout the chapters, we saw how society, law, politics, Laboratory Animal Sciences, and, as a consequence, also nonhuman animal experimentation practices remained anthropocentric. The consensus remained that it is legitimate to use nonhuman animals for human benefit (and not vice versa) when humans decide this is necessary and therefore ethically warranted. Nonhuman animals continued to be objects in a legal sense and were not considered actors when it comes to decision-making processes regarding nonhuman animal experimentation practices. In the chapters about the Polio-monkeys and the XPA-mice, we saw that this implied a foreclosure on the opportunities they had to affect larger dimensions of their lives (macro-agency) and likewise severely limited opportunities to affect the smaller dimensions of their day-to-day existences (micro-agency). Several scholars have argued that nonhuman animal experimentation and especially nonhuman transgenic animal experimentation question the human/animal dichotomy by blurring boundaries between species.[7] This thesis has shown, however, that rather than blurring species boundaries, most nonhuman animal experimentation practices reinforce these boundaries. Not only is nonhuman animal experimentation underpinned by a human/animal dichotomy, it also reproduces it through every act of experimentation and every act of permitting an experiment. This in turn leads to a further congealment of the human/animal dichotomy, making it difficult to imagine other, non-hierarchical, ways of being with other animals.

Another continuity can be found in the construction of human and nonhuman animal interests as interdependent in the discourses of "good science", 3Rs, alternatives, and "better science". Although we saw variations within these discourses, they all focused on technoscientific developments that benefited both humans and nonhuman animals, whether through improved care in the 1950s or nonanimal innovations based in human biology in the 2020s. This interdependency has however not been a symmetrical one, and the benefit for nonhuman animals questionable. For nonhuman tested animals, it has meant that their interests were only served when they were aligned with human interests (e.g., nonhuman animals were only given bigger cages and/or housed socially when this did not interfere with the experiment; in vitro methods only replaced in vivo methods when this benefited humans). In situations of a trade-off, human interests consistently prevailed over nonhuman interests. For activists and scientists this has been reason to only focus on "win-win" situations and step away from ethical debates about what should happen when interests are not aligned. Yet such approaches have resulted in a "win-win" situation only for humans, but not for other animals: either nonanimal innovations are developed which give humans "better science", or they can continue to legitimately use nonhuman animal experimentation since human needs are seen to outweigh nonhuman interests. As a consequence, nonhuman animals are rendered powerless regarding their own fates, which has been and continues to be tied up with human abilities to develop "better science".

It also became clear from the chapters that it is impossible to generalize about what these developments meant for the nonhuman animals who were used in experiments.

7 E.g., in the work of Donna Haraway, see also Chapter 1.

How these developments played out varied from species to species and, of course, also between individuals, as became clear from zooming in on the micro-level of the laboratory. The case studies of mice and monkeys showed that humans find it more difficult to objectify and de-individualize monkeys than they do mice. This affected human-monkey and human-mice relations and day-to-day interactions (e.g., interspecies play and hand rearing were much more common in intra-primate interactions). Humans favouring fellow primates also affected nonhuman lives through practices of 'replacement' as part of alternatives policy. We saw for example that rats replaced monkeys in polio vaccine testing (although this was also for economic reasons) and that the Animal Testing Act only allowed testing on nonhuman primates, cats, dogs and horses when no other nonhuman animal could be used.

On the individual level, we saw that increased attention to care and welfare and later 'refinement' as part of the 3Rs had a significant impact on the living circumstances of tested animals. For example, group housing instead of individual housing opened up all kinds of opportunities for social interactions for the Polio-monkeys. Even here, however, we have to be careful not to generalize and be mindful of differing individual experiences. For example, in both the case of Polio-monkeys and of the XPA-mice, we saw that social housing could also result in serious aggression among cage mates, sometimes even leading to death.

It was also at the individual level that the human/animal dichotomy was sometimes challenged, especially in the case of the Polio-monkeys, who were much more likely to be recognized by humans as individuals than the XPA-mice. Even in the XPA-mice case, though, species boundaries were sometimes blurred, for example when humans imagined what the gavage feeding felt like to mice or when mice resisted being objectified by biting and screaming. Yet we also saw that due to the aforementioned stabilities in interspecies power relations, response-abilities to go further than these minor challenges were foreclosed upon. These minor challenges are relevant for the aim of deconstructing a human/animal divide however, since they show that this divide is not naturally given and that work needs to be done to reproduce it.

So far, we have seen that nonhuman animal experimentation has remained a generally accepted practice. This does not mean that no efforts were made to end nonhuman animal testing, since there has also been general consensus for decades that nonhuman animal experimentation is undesirable and a 'necessary evil'. The Animal Testing Act of 1977 stated that no nonhuman animal test can be performed if an acceptable nonanimal alternative is available. Since then, the development of such alternatives has become a focus of scientists and politicians. They were promoted as the "win-win" that would benefit human and nonhuman animals alike. The case studies showed however that developing and implementing alternatives was not always a success story. The transgenic XPA-mice were meant to be alternatives for regular mice and to reduce the use of mice in carcinogenicity testing, but they were never used as such. In the case of the Polio-monkeys, the strong reduction in monkey use preceded the Animal Testing Act and alternatives policy. Eventually, the monkeys were successfully replaced by a nonanimal alternative, the Vero cell line, though much later than technically possible. Both cases showed that the successful implementation of alternatives depended on much more than the scientific quality of the alternative. In the case of the Polio-monkeys, it took an infection among the monkeys combined with difficulty to obtain new monkeys to provide the last push towards implementation of alternatives and a deci-

sive 'no' from the AEC to completely end monkey-use. Risk aversion was an important barrier to implementation in this case and also played a role in the XPA-mice case, combined with high costs and patenting issues.

Looking beyond these specific alternatives, I have shown that reductions in nonhuman animal use often were caused by many factors beyond deliberate attempts to reduce nonhuman animal testing based on ethical considerations. Looking specifically at the RIVM, we saw that the changes the institute went through had consequences for their nonhuman animal use. When the production of vaccines moved away from the RIVM to other organizations, their animal use was greatly reduced. Although the institute has 'de-animalized' (as they called it), they have found ways to hold on to their international position as a leader in the field by switching focus from high-quality nonhuman animal experimentation to developing (policy on) alternatives and international harmonisation of these policies. Currently, they play an important role in the TPI program and thus continue to play a prominent role in the field of nonhuman animal experimentation and alternatives.

FUTURE PERSPECTIVES

What do these insights mean for future perspectives and approaches to "solving" the "wicked problem"? We saw that the current TPI program of the Dutch government focuses on "better science"—good science which "by the way" needs no experimental nonhuman animals. We also saw that many activists have strategically adopted the "better science" approach as well and some are even partners in the TPI program. Within TPI, the issue of "ethics" is eschewed to avoid difficult discussions and to avoid pushing away those that still work in nonhuman animal experimentation. At the 2019 TPI conference 'Pioneer-2-Policymaker, a speaker stated that a sense of urgency is lacking. Indeed, transition experts have shown that society is not much concerned with the ethics of nonhuman animal experimentation at the moment; the 'technoscience' win-win frame has been dominant for decades.[8] In the words of Pijnappel: are we still 'lost in technification'?[9]

The focus in transition approaches is on identifying drivers and barriers on multiple levels as a basis for developing (governance) instruments that can accelerate the desired transition.[10] Within complex systems approaches to transitions it is argued that to achieve fundamental change, underlying structures and mental models need to be addressed.[11] Additionally several scholars have argued that transition studies need to

8 Natuur en Voedselkwaliteit Ministerie van Landbouw, 'Hoogleraar Rotmans: Nooit eerder zag ik de overheid een transitie aanjagen - Nieuwsbericht - Transitie Proefdiervrije Innovatie' (Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2020) <https://www.transitieproefdiervrijeinnovatie.nl/actueel/nieuws/20/07/02/hoogleraar-rotmans-nooit-eerder-zag-ik-de-overheid-een-transitie-aanjagen>.

9 M. C. Pijnappel, Lost in Technification : Uncovering the Latent Clash of Societal Values in Dutch Public Policy Discourse on Animal-Testing Alternatives ([S.l. : s.n.], 2016) <https://repository.ubn.ru.nl/handle/2066/151524>.

10 Frank W. Geels, 'From Sectoral Systems of Innovation to Socio-Technical Systems: Insights about Dynamics and Change from Sociology and Institutional Theory', Research Policy, 33.6 (2004), 897–920 <https://doi.org/10.1016/j.respol.2004.01.015>; M. J. W. A. Schiffelers, 'Animal Testing, 3R Models and Regulatory Acceptance : Technology Transition in a Risk-Averse Context', 2016 <http://dspace.library.uu.nl/handle/1874/334103>.

11 R. Cavana & K, Maani, 'A Methodological Framework for Integrating Systems Thinking and System Dy-

be more attentive towards politics and power relations and inclusions and exclusions and need to include more diverse stakeholders.[12] This attentiveness towards politics and power relations echoes the approach of scholars in critical posthumanism, political science, and critical animal studies that informed the multispecies approach taken in this thesis. Let us therefore reflect on this multispecies approach and what insights it can offer for bringing about a transition away from nonhuman animal experimentation.

I aimed to write a thesis in which humans were decentred and nonhuman animals could share the stage as embodied individuals and subjects of historical research. By 'looking for the animal in the archive' as well as in interviews and images, I have certainly been able to tell more about the lives of tested nonhuman animals in the past than I would have been able to without taking such a deliberate multispecies approach. Of course, the availability of sources limited the experiences I could describe and whose stories could form part of this thesis. There have been many nonhuman animals at the RIVM whose lives were not documented anywhere. The 'ethics of exclusion' approach and insights from political sciences have broadened what has been accounted for in this thesis. I analysed not only day-to-day interactions but also possible worlds and lives that were foreclosed on for nonhuman animals, both on the micro-level and the macro-level. It is this part of the multispecies approach that opens up avenues for rethinking the transition away from nonhuman animal experimentation.

This thesis has also shown several barriers that have stood in the way of a successful transition towards nonanimal alternatives, such as risk aversion and regulations. These are factors well known to transition scholars, and therefore the contribution of this thesis lies somewhere else. Taking a multispecies approach has shown another major factor underlying the continuities in nonhuman animal experimentation: anthropocentrism. What if we were to design our relations with other animals based on a posthumanist ethics rather than anthropocentrism? This would not magically lead to finding those highly desired "win-win" alternatives, but would definitely alter the focus of the transition away from nonhuman animal experimentation. It would raise questions such as: how can we include nonhuman animals as political actors in making decisions about experimentation? Is there such a thing as 'interspecies consent'? Is there any space at all for experimenting on nonhumans when interspecies power relations are non-hierarchical? Perhaps we could call this an 'animal turn' in transition studies and management, in alignment with the 'animal turn' in history, where both nonhuman and human animals and interspecies justice are at the heart of the transition.

You might now object that we simply *need* nonhuman animal experimentation. "Necessity" is often put forward as a justification for experimenting on other animals. However, the idea that there is a need for knowledge based on nonhuman animal experimentation is *preceded* by the premise that these experiments are justified in case we deem them necessary. Therefore, a perceived need cannot logically translate into a justification for the practice of nonhuman animal experimentation. This is why we never even think about the need for knowledge based on (forced) human experimentation,

namics. Proceedings of the 18th International Conference of the System Dynamics Society; 2000 August 6-10. Bergen, Norway. New York: System Dynamics Society; 2000'.

12 Flor Avelino and others, 'The Politics of Sustainability Transitions', Journal of Environmental Policy & Planning, 18.5 (2016), 557–67 <https://doi.org/10.1080/1523908X.2016.1216782>; Mary Lawhon and James T. Murphy, 'Socio-Technical Regimes and Sustainability Transitions: Insights from Political Ecology', Progress in Human Geography, 36.3 (2012), 354–78 <https://doi.org/10.1177/0309132511427960>.

as this is simply no longer considered an option. A change in our mental model, to stay in transition terminology, about nonhuman animals and interspecies relations towards non-anthropocentrism would not make (forced) nonhuman animal experimentation "unnecessary" but rather foreclose on it as an option.

A transition based on a posthumanist ethics would have to begin with a focus on questions of how to start changing dominant mental models (to which hopefully this thesis makes a small contribution, see also the Epilogue for a reflection on the role of art in this) and structures of democratic decision making. 'Animal rights' are often proposed by animal activists as the way to achieve justice for other animals, but they are not unproblematic. Just as "human rights" have not ended all human injustice and oppression, "animal rights" will not automatically lead to ending injustice and oppression for nonhuman animals in practice. Additionally, the concept of animal rights is criticized for being anthropocentric and problematic for seeing living beings as atomistic individuals rather than relational beings.[13] For a move beyond anthropocentrism, animal rights might be a useful temporary tool for "levelling the playing-field" but is not enough to create interspecies justice. To avoid a "humanist imposition" on other animals, it could be helpful to focus on relinquishing rights that we as humans have bestowed upon ourselves (e.g., letting go of the right to own other animals), rather than imposing rights on other animals (e.g., giving animals the right to not be property). Such legal changes in combination with a change in socio-cultural interspecies power relations would be a first step in removing structural forces that constrain nonhuman micro- and macro-agency. Only when there is more space for nonhuman macro-agency can we, humans and nonhumans together, start developing multispecies democratic practices. In such a democracy, decisions about experimentation would no longer be left to humans alone and the fate of nonhumans would no longer be depended on human abilities to develop "better science".

13 Eva Meijer, 'Interspecies Democracies', in Animal Ethics in the Age of Humans: Blurring Boundaries in Human-Animal Relationships, ed. by Bernice Bovenkerk and Jozef Keulartz, The International Library of Environmental, Agricultural and Food Ethics (Cham: Springer International Publishing, 2016), pp. 53–72 <https://doi.org/10.1007/978-3-319-44206-8_4>; Tony Milligan, 'The Political Turn in Animal Rights', Politics and Animals, 1 (2015), 6–15.

EPILOGUE

EPILOGUE

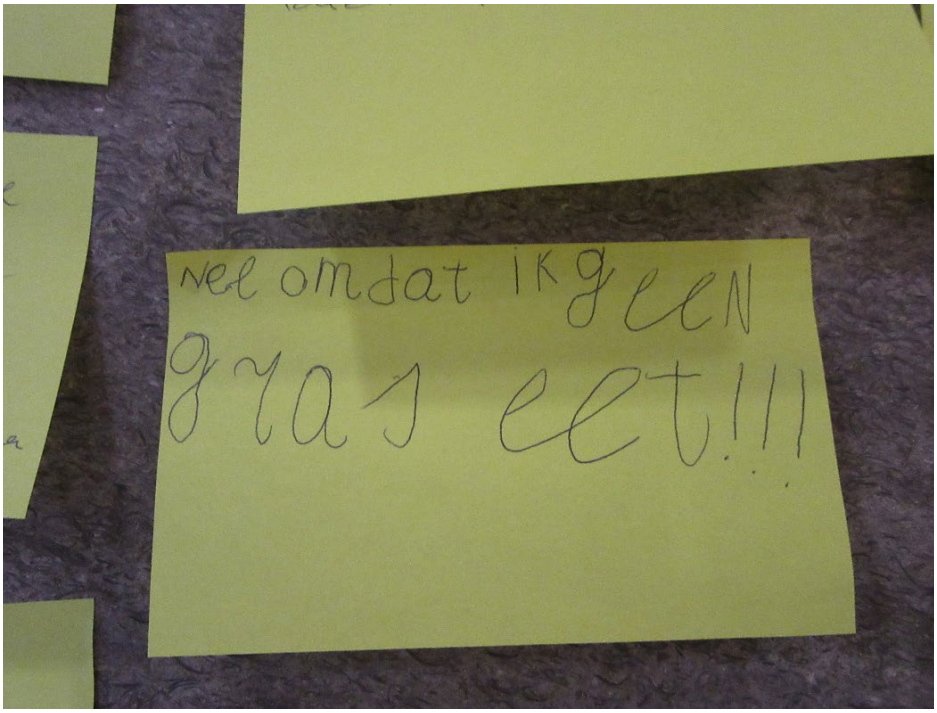

Figure E.1 'No because I don't eat grass'. Photographer: Anne van Veen

The image above shows a young girl's response to the question 'Are you an animal?': 'No because I don't eat grass'. She had contemplated several other answers, such as 'No because I can't fly', looking for something all animals have in common that humans don't. Each time she was rebutted by her mother ('dogs don't fly', 'not all animals eat grass', et cetera), but no matter how hard her mother tried to convince her that perhaps humans might be a species of animal, she stayed firm in finding this utterly ridiculous. She held this belief despite the fact that she had had no issue whatsoever playing a monkey in a cage just minutes before. Both the cage and the question were part of a performative installation about nonhuman animal testing history which I created for the 2017 'Weekend of Science', one of two artistic public engagement activities developed as part of my PhD research.

From the start of my PhD project, I felt the need to engage with the histories I studied in a more embodied and non-linguistic way than through just writing about them—unsurprisingly given my background as a dancer and choreographer. Artistic practice can function both as an investigative method and as means of communication about research. Creative practice methods are well-equipped to access what is often called tacit, embodied, or experiential knowledge.[1] As stated in Chapter 1, in the absence of

1 K. Niedderer, 'Mapping the Meaning of Knowledge in Design Research', 2007 <http://uhra.herts.ac.uk/handle/2299/4406

Figure E.2 The cage experiment: 'Are you an animal?'. Photographer: Toine Pieters

Figure E.3 The cage experiment: 'Are you an animal?'. Photographer: Toine Pieters

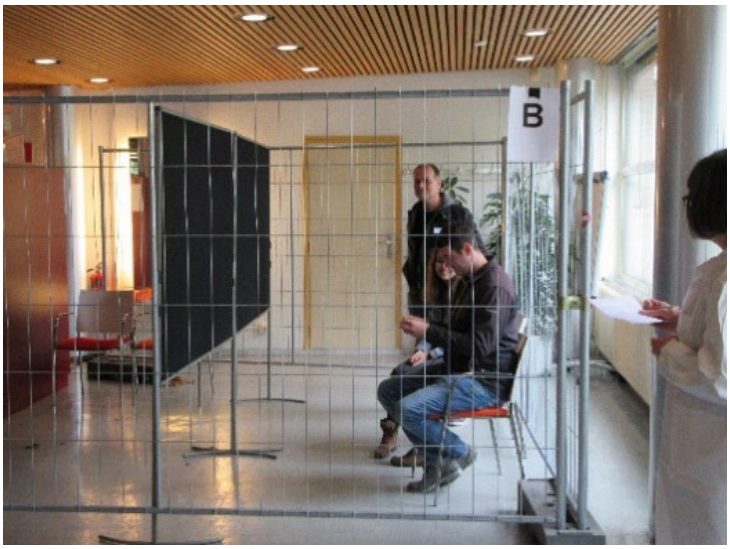

Figure E.4 The cage experiment: 'Are you an animal?'. Photographer: Toine Pieters

Figure E.5 The cage experiment: 'Are you an animal?'. Photographer: Toine Pieters

live nonhuman animals 'the animal historian must instead forge a (real, genuine, authentic, ethical) relationship with the embodied traces of past animal life'.[2] I have found

> [accessed 19 December 2016]; Kristina Niedderer and Seymour Roworth-Stokes, 'The Role and Use of Creative Practice in Research and Its Contribution to Knowledge', in IASDR International Conference, 2007, dccxcv.

2 Etienne Benson, 'Animal Writes: Historiography, Disciplinarity, and the Animal Trace', Making Animal Meaning, 2011, 3–16, 3.

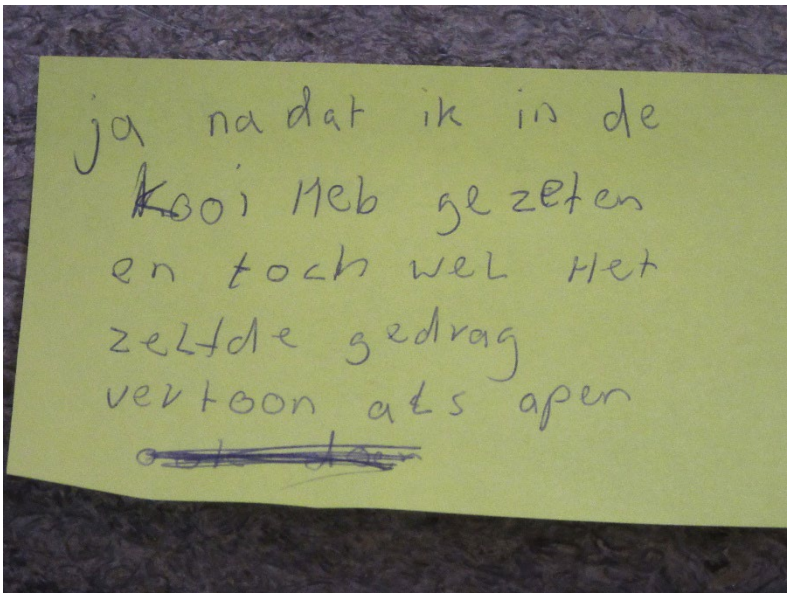

Figure E.6 'Yes, after I have been in the cage and did show the same behavior as monkeys'. Photographer: Anne van Veen

that performative methods have been useful in forging such a relationship by fostering embodied empathy towards past nonhuman animals both in myself as a researcher and in the audience. Furthermore, an artistic product has the ability to communicate findings that remain elusive to articulation, since communication can happen through experiences, as opposed to linguistic descriptions of experiences. Below I will give a brief description of the two performances and my experiences with them.

THE CAGE EXPERIMENT: 'ARE YOU AN ANIMAL?'

Figure E.7 'Not Tested on Animals'. Photographer: Juri Hiensch

This performative installation was based on the cage preference experiments performed with the Polio-monkeys at the RIVM in the 1980s (see Chapter 3). As in the original experiments, I constructed a double cage with a sluice in between, so that the humans could move between the two cages whenever they wanted to. Likewise, just as in the monkey experiment the only difference between the cages was the location of seats (chairs for the humans, perches for the monkeys): positioned either in the corner or along the side. Every half hour, a small group of humans could join the experiment. Half of the group would be the scientists observing the experiment, the other half would be experimented upon. The "scientists" had to change into clean outfits before entering the area with the cages. They were each assigned a human to observe and given a form to write down their observations (movement patterns, time spent in each cage, interactions with others, signs of distress et cetera, see Appendix 1). They could also look at drawings of the original experiment. People in the experimental group were numbered (with a sticker, not a tattoo like the monkeys) and entered the cages. They were not given any further instructions. After ten minutes, I ended the experiment and held a discussion of the experience, giving participants a chance to ask questions. I also asked everyone to answer the question 'are you an animal?' on a sticky note.

The aims of this performance were twofold. The first was to engage the public with a specific episode in the history of nonhuman animal testing. The second was to challenge people to think and feel into the meanings of "human" versus "animal" and to question the dualist thinking that we often experience as natural. Regarding the first aim, I noticed that people engaged with the history of the Polio-monkeys via their own embodied experiences. For example, one audience member told the group that he preferred the cage near the window because he could feel the sunlight there, which made

him (and others) wonder if the Polio-monkeys could also sometimes feel sunlight in their cages and whether or not they would have liked this as well. The experience was also important for their sense of what it meant to be in a cage, especially for a long time. Many participants, for example, commented that ten minutes felt like a very long time. Some participants also referred to their cage experiment when answering the question if they were an animal:

This brings us to the second aim of challenging dualist thinking. Although more research needs to be done on this, I think it is plausible that experiences such as the cage simulation which stimulate cross-species embodied empathy can put people in a state in which they are more open to critically reflect on their own assumptions regarding humanity and animality. Many people commented that this is not something they often think about. Several people also reflected on the fact that they normally use the terms "human" and "animal" as mutually exclusive, even though they had just written on the sticky note that humans are also animals (most teenagers and adults answered the question with 'yes', often referring to humans being mammals or primates). It was especially interesting to see the responses of children and the surprise of adults about those responses. Several young children participated in the experiment and found the idea that humans were animals to be very strange, as if we were making a joke—were we seriously suggesting this? Parents were generally surprised, and one mother tried very hard to convince her daughter that humans are also animals but without success. I was personally not so surprised by this, given what children learn about other animals at school, through books, at the (petting) zoo, et cetera. What we can learn from this is that it would be worthwhile to critically look at what we are teaching the next generations, which mental models we are forging, and what these potentially mean for future interspecies relations.

PERFORMANCE 'NOT TESTED ON ANIMALS'

In September 2018, the 'Meet the Future' festival was held at Utrecht Science Park, wherein which scientists collaborated with artists to create performances about their research. For this festival, I worked together with RIVM researcher Victoria de Leeuw and theatre collective De Kwekerij to create the performance *Not Tested on Animals*. The focus of this festival was more on communication about research using performance than on performance as a research method, and we were limited to a more or less traditional theatre/lecture set-up. Nevertheless, we managed to incorporate interaction and embodied experiences for the audience. In the performance, I spoke about the history of nonhuman animal testing and alternatives in the Netherlands, and Victoria explained her research on non-animal innovations in reproductive toxicology. At the same time, we submitted the audience to an experiment. When people entered, we wrote a number on their hand and assigned them to a specific seating area. At the start of the performance, the front row was selected as the "experimental group" and two "technicians" rubbed a liquid substance on the back of their hand. During the performance, we regularly checked on their wellbeing and made sure their physical environment was as refined as possible given the conditions of the experiment. Halfway through the performance, one of the audience members in the experimental group became unwell. Not to worry, this "audience member" was actually an actor. The unwell

participant was isolated from the others 'for everyone's safety' and placed in a cage on the stage. In the cage he transformed into a mouse and got angry with humans for their anthropocentrism. To challenge this anthropocentrism, he engaged the audience in a thought experiment:

> Mouse: Okay, so it is just a weighing of suffering?
>
> Scientist[3]: Yes, it is just very rational, if the benefits outweigh the suffering, then we do the experiment and if not, we don't.
>
> Mouse: Great, rational ethics! Then I am going to do something very rational as well. I am going to have a democratic vote with the audience.
>
> Scientist: Go ahead.
>
> Mouse: Yes okay. Let me ask you (to the audience): can we do an experiment on millions of mice to potentially increase the lifespan of one human with a few months?
>
> Audience: No.
>
> Mouse: No, okay great. Now let's turn this around. Can we do an experiment where we potentially shorten the lifespan of one human with a few months to save the lives of millions of mice?
>
> Audience: ???
>
> Mouse: No as well right? So, your anthropocentric nonsense makes you ethically completely inconsistent! That is the entire problem.

After that, the mouse leaves and wishes the humans good luck with their 'better science'.

Although the traditional theatre set-up was, in my experience, less suitable for creating embodied experiences and fostering cross-species empathy than the performative installation described before, the performance was an interesting first experiment with the possibilities that theatre offers in having nonhuman animals present through actors taking on the role of nonhuman animals, images and sounds rather than through actually involving living nonhuman animals. I can imagine that combining elements of both performances and developing them further could result in performances in which cross-species empathy and challenging anthropocentrism would be stimulated even more (for example, when audience members could be assigned to play or represent specific groups of nonhuman animals or technology could be used to connect with nonhuman animals, without physically bringing them into the theatre). In addition, performance can also be a place to explore interspecies democratic practices and future interspecies relations.

Unlike the mice in Chapter 6, the mouse in the performance could "vote with his feet".

3 In addition to giving a lecture (as myself) as part of the performance, I also played a scientist with decades of experience in nonhuman animal testing who does not think nonhuman animal testing should be controversial.

He could decide to no longer participate in any experiments by leaving and as such impact key factors of his life. In more abstract terms, manifestations of macro-agency were not foreclosed for him. In my Conclusion, I argued that interspecies justice requires that we start removing structural forces that foreclose micro and macro level agency of other animals. In order for this to happen, anthropocentric mental models need to change. Performances and art in general can play an important role in this in several ways: they can reach wider audiences (including young children), they can include nonhuman animals in creative ways, they can foster cross-species empathy, they can be spaces to safely experiment with new democratic practices (what if lab mice could "vote with their feet"?), and they can stimulate the imagination we need to envision radically different ways of being and becoming together with other animals.

Abbreviations
Literature & Sources

ABBREVIATIONS

3Rs	Replacement, Reduction, Refinement
AAP	Administratieve Automatisering Proefdierengebruik
ACT	Alternative to Carcinogenicity Testing
AEC	Animal Experiments Committee
AIVD	Algemene Inlichtingen- en Veiligheidsdienst
AT	Animal Technician
AVS	Anti-Vivisection Society
BBio	Bilthoven Biologicals
BPRC	Biomedical Primate Research Centre
CAD	Coordinatiepunt Alternatieven voor Dierproeven
CCD	Centrale Commissie Dierproeven
CD	Crohn's disease
CDL	Centraal Dierenlaboratorium
CPB	Centraal Proefdierenbedrijf
CvAvdD	Commissie voor Advies voor de Dierproeven
CWT	Commissie Wetenschappelijke Toetsing
DEC	Dierexperimentencommissie
ECVAM	European Centre for the Validation of Alternative Methods
EMEA	European Union Agency for the Evaluation of Medicinal Products
ERGATT	European Research Group for Alternatives in Toxicological Testing
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use.
ILSI/HESI	International Life Sciences Institute/Health and Environmental Sciences Institute
IPV	Inactivated Polio Vaccine
KNAW	Koninklijke Nederlandse Akademie van Wetenschappen
LNV	Landbouw, Natuur en Voedselkwaliteit
MAP	M. avium ssp paratuberculosis
NBBV	Nederlandse Bond tot Bestrijding van Vivisectie
NCad	Nationaal Comité advies dierproevenbeleid
NKCA	Nationaal Kenniscentrum Alternatieven voor dierproeven
NIH	National Institutes of Health
NVBD	Nederlandse Vereniging tot Bescherming van Dieren
NVI	Nederlands Vaccin Instituut
NVP	Nederlandse Vereniging voor Proefdierkunde
NVVD	Nederlandse Vereniging Vergunningshouders Dierproeven
NVWA	Nederlandse Voedsel- en Warenautoriteit
OPV	Oral Polio Vaccine
PAD	Platform Alternatieven voor Dierproeven
RIVM	Rijksinstituut voor Volksgezondheid en Milieu
RVP	Rijksvaccinatieprogramma
SAVB	Stichting Anti-Vivisectie Bond

SID	Stichting Informatie Dierproeven
SPF	Specific-pathogen-free
SVM	Stichting tot bevordering van de Volksgezondheid en Milieuhygiëne
TNO	Nederlandse Organisatie voor toegepast-natuurwetenschappelijk onderzoek
TPI	Transitie Proefdiervrije Innovatie
UMCU	Universitair Medisch Centrum Utrecht
VHI	Veterinaire Hoofdinspectie
WHO	World Health Organization
Wob	Wet openbaarheid van bestuur
WoD	Wet op de Dierproeven
XPA	Xeroderma Pigmentosa Group A

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Respondents were given the choice if they wanted to be referred to by name or anonymously. For those respondents who wished to remain anonymous, the code used to refer to them as well as their profession/expertise is listed below.

Name/code and date
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R2 (Animal Technician); 25/05/2017
R3 (Animal Technician); 20/06/2017
R4 (Expertise on polio vaccine production RIVM); 15/06/2017
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Dr. Anne Kienhuis; 14/02/2020
Dr. Annemieke de Vries; 11/06/2018
Conny van Oostrom; 11/07/2018
Dr. Harry van Steeg; 24/06/2018
Piet de With; 18/06/2018
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Dr. Martijn Dollé; 27/06/2018

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SAMENVATTING

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Dit boek gaat over de geschiedenis van experimenten op niet-menselijke dieren en de alternatieven daarvoor. De focus ligt op Nederland, met een specifieke focus op het Rijksinstituut voor Volksgezondheid en Milieu (RIVM), en de periode 1950-2020. De hoofdvraag van het onderzoek luidt:

> Hoe hebben experimenten op niet-menselijke dieren en alternatieven daarvoor zich ontwikkeld in Nederland, en specifiek bij het RIVM, in de periode 1950-2020?

Dit boek kenmerkt zich door wat ik een 'multispecies' benadering noem, waarin gepoogd wordt om op niet-antropocentrische wijze historisch onderzoek te doen. Niet-menselijke dieren worden gezien als individuen met een eigen geschiedenis, die van belang is ongeacht het belang hiervan voor de geschiedenis van mensen. De individuele ervaringen van niet-menselijke dieren die experimenten hebben ondergaan en hoe deze door te tijd heen veranderd zijn, staan dan ook centraal in dit boek. Het gaat hierbij om vragen als: Wat hebben ontwikkelingen in het experimenteren op niet-menselijke dieren en alternatieven daarvoor betekend voor de ervaringen van verschillende niet-menselijke dieren in verschillende periodes? Wat is er door de tijd heen veranderd voor niet-menselijke dieren waarop geëxperimenteerd is en wat niet? Wat hebben ontwikkelingen in wetgeving, wetenschap, politiek en de maatschappij betekend voor relaties tussen mensen en andere dieren, specifiek de 'multispecies' relaties in laboratoria?

Om deze vragen te beantwoorden is er gekozen voor een *case study* benadering. Dit maakt het mogelijk gedetailleerde aandacht te besteden aan interacties tussen dieren (inclusief mensen) op microniveau en de ervaringen van individuen. Het boek bevat de volgende casestudies: de RIVM Polio-apen, de RIVM Dierexperimentencommissie (DEC), de XPA-muizen. Ook bevat het boek een theoretisch hoofdstuk waarin de 'multispecies' benadering verder wordt uitgewerkt en een hoofdstuk waarin ontwikkelingen in het gebruik van niet-menselijke dieren in experimenten, wetgeving, wetenschap en de Nederlands samenleving in grote lijnen worden geschetst voor de periode 1950-2020. In combinatie geven de hoofdstukken meer inzicht in de recente Nederlandse geschiedenis van experimenten op niet-menselijke dieren en alternatieven daarvoor, zowel op macro- als microniveau, een onderwerp waarnaar historisch onderzoek tot nu toe nog vrijwel volledig ontbrak. Daarnaast beoogt dit boek ook bij te dragen aan de huidige discussie omtrent de transitie naar diervrije-wetenschap en relaties tussen mensen en andere dieren meer in het algemeen.

In het eerste hoofdstuk is het theoretisch kader verder uitgewerkt. Dit hoofdstuk laat zien dat de disciplines (feminist) science studies, critical animal studies, critical posthumanism en political science bruikbare concepten en analytische *tools* bieden die historici kunnen inzetten ten behoeve van het schrijven van niet-antropocentrische geschiedenissen. In combinatie benadrukken deze disciplines aandacht voor niet-menselijke dieren als subjectieve individuen, maar bovenal ook voor structuren, machtsverhoudingen en uitsluitingsprocessen en hoe deze de mogelijke levens van niet-menselijke dieren hebben beïnvloed.

Hoofdstuk 2 gaat in op ontwikkelingen in wetgeving, wetenschap, politiek en maatschappij en laat zien dat er een aantal algemene trends te onderscheiden is, zoals: popularisering van het 3V's discourse vanaf eind jaren 1970, weerstand tegen regulering van proeven op niet-menselijke dieren gevolgd door acceptatie daarvan, de intrede van 'ethiek' in het discours in de jaren 1980, het *framen* van alternatieven als een win-win voor mensen en niet-menselijke dieren. Ook laat dit hoofdstuk zien dat veel andere factoren dan bewust beleid van invloed waren op praktijken van proeven op niet-menselijke dieren. Zo zorgden een veranderd takenpakket bij het RIVM eerst voor een reductie in proefdiergebruik en later was het instituut hierdoor helemaal geen vergunninghouder meer. Alles bij elkaar genomen laat het hoofdstuk zien dat hoewel er veel is veranderd in Nederland sinds 1950 als het gaat om proeven op niet-menselijke dieren en alternatieven daarvoor, er op een fundamenteler niveau ook veel onveranderd is gebleven. Zo is antropocentrisme nog steeds alomtegenwoordig in de Nederlandse samenleving, wetgeving, politiek en wetenschap. Machtsrelaties tussen mensen en anderen dieren bleven stabiel en bleven proeven op niet-menselijke dieren legitimeren.

Hoofdstuk 3 gaat nader in op de ervaringen van een specifieke groep niet-menselijke dieren, namelijk meerdere generaties van de 'Polio-aapjes' op het RIVM, en hoe deze ervaringen zijn beïnvloed door de ontwikkelingen beschreven in Hoofdstuk 2. Vanaf eind jaren 1950 importeerde het RIVM grote groepen apen, wiens nieren werden gebruikt om het poliovaccin te bereiden. Gedurende de jaren 1960 en 1970 waren economie en volksgezondheid de belangrijkste drijfveren om veranderingen in dit gebruik te bewerkstelligen. De apen waren schaars, duur en gevoelig voor ziekte door stress en infecties. Door aanpassingen aan het vaccinproductieproces, wisten RIVM-onderzoekers het gebruik van apen steeds verder terug te dringen; daarnaast werden hygiënemaatregelen genomen om de apen zo 'schoon' mogelijk te houden. Vanaf de jaren 1980 begon 'ethiek' een rol te spelen: het reduceren van aap-gebruik en het bevorderen van het welzijn van de apen was niet alleen van economisch en volksgezondheidsbelang, maar ook een morele plicht. Apen werden niet meer gevangen in het wild, maar gefokt op het RIVM. Ook werden ze steeds vaker in groepen gehuisvest. Voor de generaties Polio-aapjes die binnen het fokprogramma werden geboren, betekende dit dat veel meer aspecten van hun leven door mensen gecontroleerd werden dan bij eerdere, wild-gevangen generaties. Het intiemer contact tussen mensen en apen maakte het lastig voor mensen om de apen te objectiveren. Ook in de maatschappij in het algemeen werd het gebruik van niet-humane primaten als problematischer gezien dan het gebruik van andere niet-menselijke dieren. Desondanks duurde het nog tot 2005 voordat de apen uiteindelijk vervangen werden door de Vero cellijn. Hoewel dit technisch gezien al sinds de jaren 1980 mogelijk was, zorgden risicomijding en een gebrek aan urgentie ervoor dat de overstap steeds werd uitgesteld. Een infectie onder de apen zorgde er uiteindelijk voor dat de stap naar de Vero-cellijn toch gezet werd, waarna de DEC het gebruik van apen ook niet meer goedkeurde.

In Hoofdstuk 4 ligt de focus op de oprichting en ontwikkeling van Dierexperimenten Commissies (DEC's) in Nederland en bij het RIVM. Zoals eerder aangetoond, werd 'ethiek' in de jaren 1980 onderdeel van het dierproeven-discours in Nederland. De samenleving en politiek eisten dat er meer verantwoording werd afgelegd over proeven op niet-menselijke dieren dan tot dan toe het geval was. Het aan wetenschappers alleen overlaten van beslissingen over de toelaatbaarheid van een dierproef, werd niet meer acceptabel geacht en de overheid besloot in 1987 om de Wet op de Dierproeven aan te

passen en een ethische afweging door een DEC wettelijk verplicht te maken voor iedere proef. De aankondiging van deze wetswijziging zorgde voor onrust onder wetenschappers, die vreesden dat deze wet catastrofale gevolgen zou hebben voor de Nederlandse wetenschap. Via een commissie van wetenschappers probeerden ze de inhoud van de wet te beïnvloeden, zodat deze zo minimaal mogelijk zou zijn en de beslissingsmacht geheel intern bij wetenschappers en vergunningshouders (voor het doen van dierproeven) zou blijven. Activisten probeerden eveneens invloed op de inhoud van de wet uit te oefenen. Zij wilden juist meer openheid en betrokkenheid van buitenstaanders, zoals verplichte 'lekenleden' in iedere DEC. De uiteindelijke wet, die in 1997 inging, was een compromis tussen beide visies, maar betrokkenheid van buitenstaanders is er niet gekomen. Ondanks initiële weerstand onder wetenschappers, werden de DEC's in de jaren die volgden een geaccepteerd onderdeel van de wetenschappelijke praktijk en namen ze een legitimerende functie aan: een door de DEC goedgekeurd experiment moest wel 'goede' wetenschap zijn, waarbij 'goed' zowel op de ethische als de wetenschappelijke aspecten van het experiment slaat. Het hoofdstuk laat echter zien dat de 'ethische toets' die DEC's behoorden te maken in de praktijk problematisch was. Richtlijnen voor deze toets waren onduidelijk en tegenstrijdig en commissies hadden de neiging om te toetsen op de wetenschappelijke kwaliteit en de toepassing van de 3V's in plaats van op ethische aspecten. De intrinsieke waarde van het niet-menselijke dier, dat op papier een centrale rol in de wet en de ethische toetsing speelde, en wat dit betekent voor de toelaatbaarheid van een experiment, kwam nauwelijks aanbod. Het kwam dan ook zelden voor dat experimenten door een DEC werden afgewezen. Toch hadden DEC's weldegelijk invloed op de levens van in proeven gebruikte niet-menselijke dieren. Het bestaan van de DEC's zorgde ervoor dat wetenschappers beter nadachten over het gebruik van niet-menselijke dieren en de 3V-mogelijheden, voordat ze een voorstel bij de DEC indiende. Bovendien vroegen DEC's wel regelmatig om aanpassingen van experimenten (bijv. het gebruik van pijnstilling). Desondanks kunnen we concluderen dat, op een abstracter niveau bekeken, de DEC's de ondergeschikte positie van niet-menselijke dieren ten opzichte van mensen juist bestendigden.

De laatste twee hoofdstukken vertellen tenslotte het verhaal van de XPA-muizen, wiens bestaan overigens gelegitimeerd werd met een verwijzing naar de 3V's. De XPA-muizen waren namelijk ontwikkeld als 'vervanging' van 'gewone' muizen in wettelijk verplichte carcinogeniteitstesten. Hoewel ze uiteindelijk nooit gebruikt zijn in deze carcinogeniteitstesten, waren deze muizen wel van grote waarden voor bepaalde mensen en het RIVM in het algemeen, doordat ze mogelijkheden creëerden voor nieuw (gesubsidieerd) onderzoek. Hoofdstuk 5 laat zien dat het niet alleen aan technisch-wetenschappelijke factoren lag dat de XPA-muizen nooit gebruikt zijn zoals vooraf bedacht. Ook factoren zoals kosten en patenten speelden hierbij een rol. Het verhaal van de XPA-muizen is ook een voorbeeld van hoe de opkomst van transgene niet-menselijke dieren zorgden voor een toename in 'in voorraad gedode niet-menselijke dieren', doordat er tijdens het fokproces veel niet-menselijke dieren geboren werden met een onbruikbaar genotype. In Hoofdstuk 6 zien we meer van de leefwereld van de XPA-muizen en hun (on)mogelijkheden om invloed hierop uit te oefenen. Een analyse van de 'choreografie van het laboratorium' laat zien dat muizen net als apen niet alleen als 'materialen' werden gezien door mensen. Zorg en *attunement* waren belangrijke onderdelen van de muis-mens relatie en stonden niet alleen in dienst van de wetenschappelijke kennisproductie. Het hoofdstuk laat echter ook zien dat ongelijke machtsrelaties ervoor

zorgden dat veel mogelijkheden voor muizen om hun eigen leven te beïnvloeden bij voorbaat al waren afgesloten. De ruimte voor muizen om weerstand te bieden aan hun 'proefdierstatus', bijv. door te bijten, was zeer beperkt en mogelijkheden om belangrijke aspecten van hun leven te beïnvloeden (zoals het wel of niet gebruikt worden in een experiment) waren er helemaal niet. Wanneer we naar de wetgeving kijken, zien we dat het antropocentrische karakter hiervan de mogelijkheden van XPA-muizen voor het uitoefenen van agency op microniveau zeer beperkte en op macroniveau geheel uitsloten, doordat XPA-muizen niet werden erkend als politieke actoren die in potentie zouden kunnen deelnemen aan democratische besluitvorming.

De hoofdstukken leiden gezamenlijk tot drie overkoepelende conclusies. Ten eerste laten ze zien dat er, ondanks dat er allerlei ontwikkelingen hebben plaatsgevonden, belangrijke continuïteiten zijn met betrekking tot experimenten op niet-menselijke dieren in de periode 1950-2020. Het is een veelgehoorde uitspraak dat er 'ontzettend veel veranderd is' als het gaat om dierproeven en alternatieven in Nederland. Daarmee wordt dan meestal verwezen naar de 3V's, het invoeren wetgeving en van DEC's die een ethische toetsing uitvoeren, de toegenomen aandacht voor het welzijn van niet-menselijke dieren. Dit boek laat echter zien dat er ook veel zaken onveranderd of slechts oppervlakkig veranderd zijn. Zo zien we in elk hoofdstuk terug dat de samenleving, wetgeving, politiek en (proefdierkundige) wetenschap antropocentrisch van aard bleven. De consensus onder mensen dat het gelegitimeerd is niet-menselijke dieren te gebruiken voor menselijk voordeel wanneer mensen dit noodzakelijk achten, is de gehele periode overeind gebleven. Ook bleven niet-menselijke dieren objecten in wettelijke zin en werden ze in bredere zin niet beschouwd als actoren die deel zouden kunnen nemen aan besluitvormingsprocessen omtrent experimenten op niet-menselijke dieren. Als gevolg hiervan bleven de mogelijkheden die proefdieren hadden voor het uitoefenen van *agency* zeer beperkt op microniveau en uitgesloten op macroniveau. Hoewel sommige wetenschappers stellen dat experimenten op niet-menselijke dieren (en dan met name transgene dieren) zorgen voor een vervaging van grenzen tussen mensen en andere dieren, laat dit onderzoek zien dat proeven op niet-menselijke dieren de grens tussen mensen en andere dieren juist versterkten, doordat deze telkens gereproduceerd werd: in elke experimentele handeling en elke keer dat er toestemming werd gegeven voor een experiment op basis van antropocentrische wetgeving.

Ten tweede laat dit boek zien dat het onmogelijk is om algemene uitspraken te doen over wat ontwikkelingen op macroniveau hebben betekent voor de niet-menselijke dieren die gebruikt zijn in experimenten. Door in te zoomen op het microniveau van het laboratorium zien we dat de uitwerking van deze ontwikkelingen verschilden van individu tot individu, afhankelijk van factoren als diersoort en persoonlijke voorkeuren. Zo kon het 3V's beleid voor een aap betekenen dat ze niet meer gebruikt werd in een proef (of überhaupt niet geboren werd), omdat ze vervangen werd voor een rat. Op deze rat had dit beleid dan natuurlijk een omgekeerd effect. Ook verrijkingsbeleid zoals groepshuisvesting had verschillende uitwerkingen voor verschillende individuen. Hoewel voor de meesten deze sociale vorm van huisvesting bevorderlijk was voor het welzijn, kwam het ook voor dat sociale huisvesting leidde tot agressie met soms zelfs de dood als gevolg.

Tenslotte laat dit onderzoek zien dat er al lange tijd consensus bestaat dat wetenschap idealiter zonder experimenten op niet-menselijke dieren wordt gedaan, maar dat het lastig bleek dit ideaal te bereiken. Bovendien was er geen consensus over of en hoe dit ideaal bereikt zou kunnen en moeten worden. Sinds de jaren 1980 is de ontwik-

keling, en later ook de validatie en implementatie, van alternatieven een expliciet beleidsdoel in Nederland. Alternatieven werden gepromoot als een 'win-win' voor mens en niet-menselijk dier. In de casestudies is laten zien dat pogingen tot het ontwikkelen en doorvoeren van alternatieven niet altijd succesvol zijn en/of heel erg lang kunnen duren. Ook werd duidelijk dat dit niet uitsluitend lag aan technisch-wetenschappelijke factoren, maar dat zaken als risicomijding, (gebrek aan) urgentie en kosten ook een rol speelden. Meer in het algemeen laat het boek zien dat bij het verminderen van het aantal proeven op niet-menselijke dieren meer factoren een rol speelden dan alleen bewust verminderingsbeleid. Zo speelde bij het RIVM, waar het aantal experimenten sterk verminderde, de verandering van taakstelling van het instituut een belangrijke rol in deze vermindering.

De hierboven beschreven verkregen inzichten geven aanleiding om vanuit een andere blik dan gebruikelijk naar de transitie richting diervrije wetenschap te kijken. In het huidige beleid wordt vooral gefocust op 'betere wetenschap', wetenschap die beter is omdat deze relevanter is voor de menselijke situatie door het gebruik van methoden die voorspellender zijn voor de mens dan methodes die gebruik maken van niet-menselijke dieren. Dat deze methoden bovendien geen niet-menselijke dieren meer gebruiken is mooi meegenomen, maar niet de hoofdfocus van het beleid. Zowel in dit onderzoek als in andere onderzoeken, is een aantal barrières naar voren gekomen die deze transitie in de weg staan. Daarnaast wijst dit onderzoek echter op een meer fundamentele factor die bijdraagt aan de continuering van proeven op niet-menselijke dieren: antropocentrisme. Dit roept dan ook de vraag op wat het zou betekenen als we onze relaties met andere dieren zouden vormgeven op basis van een posthumanistische in plaats van antropocentrische ethiek. Dit zou er niet toe leiden dat we opeens alle zo gewenste 'win-win' alternatieven op korte termijn zouden kunnen ontwikkeling, maar zou er wel toe leiden dat we op een andere manier over proeven op niet-menselijke dieren nadenken, waardoor het ontwikkelen van deze alternatieven geen voorwaarde meer is om te stoppen met (onvrijwillige) proeven op niet-menselijke dieren. Wanneer we dit perspectief combineren met recente inzichten uit de politieke filosofie over 'interspecies democracy', kunnen we gaan nadenken over hoe we besluitvormingsprocessen zo kunnen vormgeven dat niet-menselijke dieren niet langer uitgesloten worden als politieke actoren. Hiervoor is het nodig dat er ruimte komt voor de micro- en macro-agency van niet-menselijke dieren, wat betekent dat structuren die deze agency tot nu toe beperkten (zoals machtsverhoudingen in de wet en daarbuiten) zullen moeten veranderen in faciliterende structuren. Alleen dan kunnen we toewerken naar een democratie waarin mensen niet meer beslissen over andere dieren en waarin het lot van (toekomstige) 'proefdieren' niet afhangt van de menselijke mogelijkheid om 'betere wetenschap' te ontwikkelen.

Acknowledgements
Curriculum Vitae

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CURRICULUM VITAE

Anne van Veen (1986) was born and raised in Nieuwegein, where she obtained her high school diploma in 2001 at the Oosterlicht College. Subsequently, she completed a Bachelor of Science in Interdisciplinary Social Sciences at Utrecht University (2006). She continued her education with training in Dance (ArtEZ/Creative College, 2011) and a Master of Art in Arts Policy and Management (Utrecht University, 2011). After graduating, she worked as an independent dance artist. In 2016, she started her PhD at the Freudenthal Institute of Utrecht University, researching histories of nonhuman animal testing and alternatives in the Netherlands (1950-2020). This research project was funded by the RIVM. During her PhD, Anne presented her research at various (international) conferences and in published articles. In addition, she used her experience as an artist to develop performances about her research. Teaching formed an important part of her PhD and Anne obtained her UTQ (BKO-w) in 2020. In April 2021, Anne started working as a postdoctoral researcher at Radboud University, where she researches the governance of accelerating the transition to a sustainable food system in the Netherlands.

OF MICE, MONKEYS & BETTER SCIENCE tells the stories of a few of the nonhuman animals that were used in experiments in the Netherlands between 1950 and 2020 through a historical analysis of three case studies: the XPA-mice, the Polio-monkeys and the Animal Experiments Committees. Moving back and forth between the micro-level of the laboratory and macro-level developments in law, society, politics, and science, this book accounts for both individual experiences and structural forces, as well as how these impact one another. Together, the case studies identify several major developments during the time period studied, which had a great impact on the lives of the individual nonhuman animals used in experimentation. At the same time, this book shows that these developments took place within a context of continuous unequal interspecies power relations and anthropocentrism and reflects on what these continuities have meant for the nonhuman animals studied and for the possibilities of transitioning away from nonhuman animal experimentation in the future.