

Moving Towards Non-Animal-Based Methods:

An Embedded Case Study on Wageningen University into Path Dependency, Lock-In, and Institutional, Technological, and Normative Barriers and Facilitators regarding the Transition Towards Non-Animal-Based Methods in the Research and Innovation Industry in the Netherlands.

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Summary

How do institutional, technological, and normative barriers and facilitators influence the current practices to transition towards non-animal-based methods, that is defined by path dependency and lock-in, in the context of the animal-based research and innovation industry in the Netherlands? This study explores and builds upon the concepts of institutional, technological, and normative barriers and facilitators, path dependency and lock-in, to answer this question. This study is executed to fill the literature gap that exists on animal welfare in the field of animal-based research and innovation by obtaining insights into what barriers and facilitators are visible and how they influence the current practices in the transition towards non-animal-based methods. This study is accomplished by employing an embedded case study based on the Wageningen University & Research combined with expert interviews in the field. Based on a qualitative analysis of the various available (policy) documents, and semi-structured interviews, it can be derived that while animal experimentation is still considered the "gold standard" in the scientific community, there are advancements in for instance computer models and laboratory experiments that yield better results. Due to the high cost and the difficulty of replacing animal-based experiments, these practices have become locked in and path-dependent. Despite the availability of advanced alternatives, the current technological structures have remained superior for an extended period. Institutional barriers and facilitators influence these current practices and developments, for instance by prioritizing minimizing animal suffering and maximizing animal welfare. Technological opportunities drive forward the transition towards non-animal-based methods. However, there are technological limitations, and complete comprehension and successful replication of interactions between different systems of a whole animal have proven to be a complex task. Furthermore, changing ethical concerns act as a normative facilitator for a transition towards non-animal-based methods. Various interlinkages suggest that institutional barriers and facilitators can influence the normative barriers and facilitators and in turn, normative barriers and facilitators can shape the institutional barriers and facilitators. The institutional and normative barriers and facilitators can in turn both challenge and influence technological opportunities and limitations or can be challenged and influenced by technological opportunities and limitations. Identifying the various barriers and facilitators, their interlinkages and their influence is a first step. Conducting a follow-up study focussing on how to overcome the barriers and enhance the facilitators could be the next valuable step to facilitate the transition towards non-animal-based research and innovation, which would be highly interesting for both scholars and practitioners in the field.

Preface and Acknowledgements

This thesis marks the end of my master's study at the Radboud University in Nijmegen and the beginning of a new, exciting chapter. Ever since I was little, animal welfare has been a central theme in my life. However, since I had chosen a certain path during middle school, I started studying Business Administration in Nijmegen. During and after my bachelor's degree, I started to focus more and more on sustainability for people, the environment and animals. During my master's study in Environment & Society Studies, I gained a lot of experience in working with policy issues on a national and international level. Yet, I still strongly missed the part of animal welfare in the sustainability subjects of my master's specialization in Global Environment and Sustainability. So, I chose to write a thesis focused on the various barriers and facilitators visible in the transition to non-animal-based innovation and to follow a (work) internship as a Program Assistant Farming at World Animal Protection, an NGO that is committed to protecting (endangered) animal species and reducing animal suffering, where I also worked as a Program Assistant Wildlife for another six months. Although the choice to start working without completing my thesis has been challenging, I would not have chosen otherwise, given all the lessons I have learned during this process. I, therefore, now, want to give my gratitude to those who supported, inspired and challenged me during this process.

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1. Introduction

In numerous scientific and medical achievements of the past century, animal-based research has played a critical role (Bressers et al., 2019). Across several fields, including “fundamental, biomedical, toxicological, behavioural, military, and agricultural research” animal-based models are used (McLeod & Hartley, 2017). Animals are generally used to check whether an intervention will cause damage to human beings or different animals of the same or other species, i.e., safety testing; or whether the intervention has the desired effect, i.e., efficacy testing (Taylor, 2019).

In the Netherlands, an average of 450,000 animal experiments are performed each year (Proefdiervrij, 2021). Most of these tests are performed on mice for scientific research, however, there are various other laboratory animals that are used such as rabbits used in safety research or dogs that are used for educational purposes (Proefdiervrij, 2021). In total, more than 30 different animal species are used in scientific research in the Netherlands every year (Proefdiervrij, 2021).

The largest number of animal tests are conducted for scientific research, followed by legally required toxicology and safety testing (Proefdiervrij, 2022). In addition, animal experiments are also carried out for educational purposes, breeding and the protection of the environment and animal species (Proefdiervrij, 2022). About 25% of all animal tests are legally required toxicity and safety tests. The other 75% of all animal experiments are not legally required, such as curiosity research and applied research (Animal Rights, 2020). Moreover, approximately 10% of all animal testing is research for intensive livestock farming (Animal Rights, 2020).

The use of animals in experiments has been a standard practice for hundreds of years. In 1981, the number of animal experiments in the Netherlands was first recorded and this was proven to be more than one and a half million (Proefdiervrij, 2021). With the help of several technological developments and scientific knowledge, the number of animal experiments has been reduced by more than half to 448,798 in 2020. Still, in contrast to 2019, this number increased. (Proefdiervrij, 2021). Furthermore, the most recent numbers show that in 2021 in the Netherlands 477,970 animal tests were performed, which is 29,172 animal tests more than in 2020 (Proefdiervrij, 2023). An increase in the number of animal experiments conducted can thus be observed.

As Penningnieuwland (2021) mentioned countless individuals are not aware that laboratory animals are often no longer necessary in research. It is considered that there are

alternatives that make animal testing superfluous (Peningnieuwland, 2021). Scientists, entrepreneurs, and social organizations perceive various opportunities for research and testing without animals (Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2021). To investigate new medicines or chemical substances for safety and efficacy with, for example, cells in a culture glass, organs on a chip, big data, artificial intelligence, and computer models is already achievable (Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2021).

However, “despite aspirations to substitute animal experimentation with alternative methods and recent progress in the area of non-animal approaches, there is no extensive replacement of animal-based research” (Lohse, 2021). As Daneshian, et al., (2010) mentioned huge numbers of animals are used in tests that may not be relevant for increasing safety of humans, due to the hesitant emergence and high inertia of regulatory toxicology, academics still must struggle with inflexibilities in this field.

Multiple researchers, organisations, and initiatives such as Proefdiervrij, Animal Rights, and Transitie Proefdiervrije Innovatie have expressed their concerns about animal-based research in the research and innovation industry in the Netherlands. Animal Rights (2020) concluded that mainly young laboratory animals, but also pregnant animals are deliberately made sick and eventually killed during the research.

Moreover, for 1 in every 100-laboratory animal in animal-based research, the experiments are so severe that they fall into the highest pain category (Animal Rights, 2020). In the Netherlands, the NVWA (Nationale Voedsel- en Waardenautoriteit) regularly carries out inspections at centres for animal-based research, even though in 60% of the cases these inspections are announced beforehand (Animal Rights, 2020). Therefore, one might argue that these inspections do not always reflect the actual reality.

Furthermore, it is said that 9 out of 10 medicines developed through animal testing are not effective or safe for humans (Peningnieuwland, 2021). As Bressers et al., (2019) described the “ethical issues associated with using animals and increased concern regarding animal wellbeing, together with concerns regarding the translatability of animal models and practical difficulties of using animals, are gaining importance” (p. 2). Concerns about these practices are not new, for instance already in 2008, it was demonstrated by public opinion surveys in developed countries that concern about the welfare of animals has grown over the last 30 years (Frank, 2008).

1.1 Research Problem

Despite the concerns described above it can be argued that the animal-based research and innovation industry is fixed in its current patterns of behaviour by consistently preferring animal-based methods over already available alternatives. Being fixed in current practices can ultimately lead to a certain path dependency and sequentially a lock-in effect. Therefore, it is highly significant to evaluate the reasons behind this current pattern and what barriers and facilitators are evident in the animal-based research and innovation industry in the Netherlands. By ultimately identifying the distinct forms of institutional, technological, and normative barriers and facilitators, that all have an influence on the transition towards non-animal-based methods.

1.2 Research Aim & Questions

This research is conducted in order to gain valuable insights into the roles of institutional, technological, and normative barriers and facilitators that are detectible in the context of the animal-based research and innovation industry in the Netherlands, regarding the usage of nonhuman actors and their welfare in the current practices, that influence the transition towards non-animal-based methods. This research aims to elaborate upon the topic of institutional, technological, and normative barriers and facilitators, in the context of the animal-based research and innovation industry in the Netherlands, and upon the concepts of path dependency and sequential lock-in effect visible in the transition towards non-animal-based methods. Thus, this study is conducted to investigate how these barriers and facilitators influence the current practices regarding the transition towards non-animal-based methods. Furthermore, this study aims to create a deeper awareness of nonhuman actors and their welfare. This research is written to answer the following research question with associated sub-questions:

How do institutional, technological, and normative barriers and facilitators influence the current practices in the context of the animal-based research and innovation industry in the Netherlands, which is defined by path dependency and lock-in, in the transition towards non-animal-based methods?

- How can the current practices of the animal-based research and innovation industry regarding nonhuman actors be described?

- What are the developments in the animal-based research and innovation industry to move towards non-animal-based methods?

- How are path dependency and the lock-in effect regarding the usage of nonhuman actors and their welfare related to the animal-based research and innovation industry?

- What are the institutional, technological, and normative barriers and facilitators that influence the current practices of the animal-based research and innovation industry to transition towards non-animal-based methods?

1.3 Societal & Scientific Relevance of the Research

In our current society focussed more and more on sustainable development, innovation, and research, the focus on animal welfare in the field of the research and innovation industry is regularly disregarded (Rollin, 2011). The public is generally not aware that the use of laboratory animals is in most cases no longer necessary in research and that there are alternatives that make animal testing superfluous (Peningniewland, 2021). Writing this thesis about the several institutional, technological and normative barriers and facilitators that are detectable in the transition towards non-animal-based methods is relevant from an ethical, animal welfare, science and regulatory perspective.

Understanding the several distinct barriers and facilitators can help with making sustainable choices in the research and innovation industry in the Netherlands, with positive implications for animals, science, and society. This enhances both the societal as scientific relevance of this research. Moreover, policies and support structures can be created to promote the adoption of non-animal-based methods and drive scientific progress when the barriers and facilitators are distinguished. Adding to this, policymakers can as a result then take more effective measures to reduce the use of animal testing and promote alternatives.

Additionally, the fact that there are alternatives that make animal-based methods superfluous highlights the societal relevance, it is to say that, to enlighten one on the institutional, technological, and normative barriers and facilitators detectable in the animal-based research and innovation industry in the Netherlands in order to create awareness for nonhuman actors and their welfare is of importance. Creating awareness among the public on feasible non-animal-based methods and the barriers that keep away the transition towards these methods could potentially create pressure from society in order to catalyse action taken in the research and innovation industry in the Netherlands.

Moreover, this thesis will shed light on the institutional, technological, and normative barriers and facilitators as observable in the research and innovation industry in the Netherlands which could be of use to all stakeholders in this industry such as the Ministry of Agriculture, Nature and Food Quality, organizations conducting animal-based research and organisations such as Proefdiervrij, since by knowing the various reasons and their influence, specific measures can be taken to ultimately empower these facilitators and overcome these barriers.

Furthermore, for several countries, reducing the number of animals used in the field of research and innovation has become a priority for their governments (Bressers et al., 2019). Governmental priority shifts increase both societal and scientific relevance since pressures to transition towards non-animal-based methods will ask for a call to action and (scientific) knowledge on the influence of these barriers and facilitators. Elaborating on the institutional, technological, and normative barriers and facilitators of the research and innovation industry in the Netherlands regarding the change of the usage of nonhuman actors and their welfare could therefore contribute to the academic knowledge in this field.

Not the least important, scientific research contesting the current behaviour of the research and innovation industry in the Netherlands towards nonhuman actors and their welfare could be valuable in the academic field. Since at this moment, most research in the domain of animal welfare is done in the field of farm animals and livestock or for practices of zoos (Sherwen, et al., 2018; Bertocchi et al., 2018; Narayan et al., 2021). This thesis will contribute to the academic literature on animal welfare in the field of animal-based research and innovation and therefore could potentially bridge a gap in current literature as well as enrich the already existing academic knowledge on the topic of animal welfare and animal-based research and innovation. Furthermore, given the relevance of societal factors for the adoption of non-animal-based methods, the absence of an understanding of the institutional, technological and normative barriers and facilitators in the context of the animal-based research and innovation industry constitutes an important research gap. This thesis, therefore, is written to fill this gap in the literature.

2. Literature Review and Theoretical Framework

First, this chapter provides background literature on animal ethics, new approached methods and the current practices and developments of the animal-based research and innovation industry in the Netherlands. This in turn is then followed by background literature on transitions, change and stability. Next, the concepts of path dependency and lock-in are elaborated upon. Then, the concepts of institutional, technological, and normative barriers and facilitators to change are explained, which is then followed by the illustration and clarification of the conceptual model. Ultimately, the operationalization of the concepts follows all the above.

2.1 Animal Ethics

Numerous human practices presume that nonhuman animals have limited, if any, rights (Pluhar, 2012). However, in recent decades, animal rights movements have gained a wide following (Fried, 2022). Generally, animal rights groups argue that “the use of animals for food, adornment (furs, leather, etc.), labour, and scientific research constitutes unjustifiable violence against our fellow living beings, who have the same rights to life and liberty as we do” (Fried, 2022). It is argued that animal rights, or more precisely nonhuman animal rights, would thus entitle certain nonhumans to civil handling by moral agents, i.e., human beings (Pluhar, 2012). Furthermore, the animal welfare approach entails that we should handle animals in a more "humane" approach and that we prohibit "unnecessary" distress (Francione, 2003).

The animal rights academic Rollin advocates for a “consensual and communitarianist ethic toward animals which translates, in welfare terms, to allowing them to function and live according to their distinctive animalian natures or ‘telos’” (Buller, 2009). This approach entails that animals should not merely be used for human benefit instead one should consider their natural needs and behaviours. By means of this approach, one can argue that using nonhuman animals for scientific research goes against their rights and distinctive nature.

Additionally, animal rights academic Regan claims that any institutionalized exploitation of nonhumans is morally unacceptable (Francione, 2003). Regan unequivocally and without ambiguousness criticizes the use of animals for food, testing, education, research, hunting and trapping (Francione, 2003). Regan believes that humans and nonhumans are subjects of life that have equal inherent value (Francione, 2003). This means that in Regan’s belief animals are not merely objects or resources for humans to use but actual beings with their own experiences, interests, and moral worth. As such, Regan argues that their interests

should be considered and respected, and they should not be treated merely as means to human ends.

In his book *Animal Liberation*, Singer argues that when assessing the consequences of our actions, including those affecting animals, we must take the interests of animals seriously and consider any negative impact of human actions on those interests as part of the consequences of those actions (Francione, 2003). We should, therefore, be sensible of the effects that our actions have on nonhuman animals and acknowledge their interests and well-being as important ethical considerations.

2.2 New Approached Methods

Currently, animal testing is widely used to assess the potential hazards, uses, and environmental impacts of chemicals (National Academies of Sciences, et al., 2022). Over the past years, an increasing number of New Approached Methods (NAMs) have been developed with the fundamental goal of providing a system that is more ethical, more efficient, and scientifically better (Schmeisser et al., 2023).

NAMs are “technologies and approaches that can make informed hazard and risk assessment decisions without the use of laboratory animals” (National Academies of Sciences, et al., 2022). These methods can include “the use of computer-based (computational) models, modernized whole-organism assays or assays with biological molecules, cells, tissues or organs, as well as exposure prediction approaches” (Health Canada, 2023).

The 3R principles of replacing, reducing, and refining standard animal experiments are followed by the development of NAMs and their use for risk assessment (Schmeisser et al., 2023). NAMs can therefore largely be defined as “alternative or complementary methods to or an enhancement of traditional animal testing to predict the hazardous properties of chemicals” (Schmeisser et al., 2023).

Furthermore, it is argued that NAMs need to be “fit for purpose, reliable and, for the assessment of human health effects, provide information relevant to human biology” (van der Zalm, et al., 2022). Because of their potential to efficiently and reliably generate information that is fit for purpose while reducing animal use, new approach methodologies (NAMs) are progressively being used for regulatory decision-making by agencies worldwide (Stucki et al., 2022).

The importance of NAMs is underlined by the fact that NAM data can be used to enhance the datasets that are studied in both ecological and human health risk assessments (Health Canada, 2023). Moreover, our understanding of how a chemical or mixture causes

toxicity can be improved by the mechanistic nature of NAM data (Health Canada, 2023).

Additionally, greater human or ecological relevance can be provided by the data of NAMs in comparison to standard toxicity tests conducted using animals (Health Canada, 2023). For example, cell- and organ-based approaches, in contrast with animal studies, allow for the use of human tissues, and consequently, data obtained from these NAMs may be more significant in informing human health risk assessments (Health Canada, 2023).

2.3 Current Practices and Developments in the Animal-Based Research and Innovation Industry in the Netherlands

The Dutch government aims to establish the Netherlands as a pioneer in cruelty-free innovation by 2025 through a transition towards non-animal-based research (Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2016). The National Committee for the Protection of Animals Used for Scientific Purposes believes that the current safety levels can be maintained even as the use of animal testing for mandatory safety tests for chemicals, food ingredients, pesticides, and medicines is gradually phased out by 2025 (Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2016).

Over the last two decades, there have been numerous scientific innovations in non-animal approaches to replace the use of animal experiments (Lohse, 2019). Four approaches are widely discussed and used.

First, the classical *in vitro* methods can use human or non-human animal cell lines to study the effects of pharmacological and other chemicals in a petri dish (Butzke et al., 2013).

Second, tissue engineering strategies are used to assemble complicated layers of human tissue or mini-organoids (miniaturised organ-like structures) to investigate physiological processes or the consequences of biomedical interventions in a greater realistic environment (Rossi et al., 2018).

The third approach to replace animal experimentation involves the usage of computer technology, the so-called ‘*in silico*’ methods. Here, virtual models are used to “study human organ systems or the toxicological properties of substances based on their chemical structure, sophisticated “read-across”-computer algorithms use large data sets of known chemical substances to predict the properties of new chemical substances with unknown properties” (Roberts et al., 2008).

Lastly, organ(s)-on-a-chip technology uses microfluidic 3D-culture chips to emulate organ structures or multi-organ structures (Lohse, 2019). Lohse (2019) explains that “advanced

biochips of this kind have miniaturised compartments with different types of cells/tissue (e.g., liver and lung cells) that are connected via microchannels allowing for circulation between “organs” (p.43). In order to, amongst others, study interactions between multiple organs over time, drug development and disease modelling purposes, these kinds of microsystems can be used (Zhang et al., 2018).

To guarantee that animal experiments are only applied when strictly necessary, research institutions in the Netherlands are working on what is called the ‘3R policy’. Whenever it is possible, research institutions attempt to “replace animal testing with alternatives, reduce the number of laboratory animals, and refine research in order to keep animal suffering or discomfort to a minimum” (Universities of The Netherlands, n.d.).

Additionally, an initiative called the ‘Transition Programme for Innovation without the use of animals’ (TPI: Transitie naar Proefdiervrije Innovatie) a collaboration between, amongst others, the national government of the Netherlands, Stichting Proefdiervrij and the Nationaal Comité advies dierproevenbeleid (NCad) departed in 2019 (Ministerie van Algemene Zaken, 2021). Within this initiative, all stakeholders work together, beyond the shared ambition of animal welfare and replacing animal experiments, by responding to and accelerating developments in the field of science and innovation (Ministerie van Algemene Zaken, 2021). Despite the innovations, stakeholder activities, and policy measures, there is currently no extensive replacement for animal experimentation.

2.4 Transitions, Change and Persistence

There has been a long-standing discussion about transitions, change and stability (Vennström & Eriksson, 2010; De Haan & Rotmans, 2011; Schlossberg, 2011). These days we collectively realise that “the way the world around us works is not the way it will work, nor the way it once worked” (De Haan & Rotmans, 2011). The systems that we have created to meet our social needs may appear stable, but sometimes that apparent stability is disrupted to give way to a new apparent stability in systems that function differently (De Haan & Rotmans, 2011). For instance, the way we currently meet our needs for energy, mobility, or how we organize our healthcare might appear given, but history shows that these systems functioned differently at one point in time and this suggests that in the future, such systems may go through fundamental changes again (De Haan & Rotmans, 2011). In the case of the research and innovation industry, using nonhuman animals for research and innovation purposes might appear as given but history shows that over time this has seen fundamental

changes as well, it is therefore highly valuable to investigate these changes and what factors influences these shifts.

Societies are faced with numerous challenges that ask for continuous modifications, adjustments, new interpretations or even drastic transformations of ongoing institutions as Kaufmann and Wiering (2021) explain. “If a societal system goes through such a fundamental change it is said to go through a *transition*” de Haan and Rotmans (2011) explain further. It is therefore important to better understand how transitions work, how to prepare, to influence or to simply know what is happening (De Haan & Rotmans, 2011).

Prior to a transition, Rotmans (2013) argues, a dominant regime exists in society. This regime can be seen as a system of customs, rules, values, norms and interests, that is aimed at maintaining and improving the functioning of the current system instead of structurally changing it (Rotmans et al., 2001). At the same time, there are so-called niches, consisting of individuals or groups with different, deviant and innovative schools of thought and perspectives that aim to transform the system (Ministerie van Infrastructuur en Waterstaat, 2022). This contradiction leads to friction, with the regime usually succeeding in preserving the current system. Sometimes, however, a tipping point occurs, in which the interaction between the regime and such a niche unleashes a transition (Ministerie van Infrastructuur en Waterstaat, 2022). Since the Netherlands aim to become a pioneer in cruelty-free innovation by 2025 through a transition towards non-animal testing research, it is highly relevant to understand what influences the state of friction either by preserving the current system or creating a tipping point.

Institutional changes are rather complex (Kaufmann & Wiering, 2021). Coalitions of actors may have different interpretations of reality or might fight for different interests (Kaufmann & Wiering, 2021). Furthermore, path dependency mechanisms may impede change, or new policy tools may not be as effective, or they could have unintended consequences (Kaufmann & Wiering, 2021). Rotmans (2013, p. 236) defines a transition as “a fundamental change in the structure, culture and working methods of a social system”. A social system is a broad concept here, which, depending on the transition in question, can refer to, a specific sector, a region or city, or even to an individual company. Structure refers to relatively observable things, such as the institutions, the economy and the physical environment of a system, for the scope of this research referred to as institutional aspects (see 2.6). Culture, on the other hand, is about ideas, shared assumptions, values and perspectives. The working method is in between, and concerns customs, rules, behaviour and daily practice (Rotmans, 2013), for the scope of this research combined with culture referred to as

normative aspects (see 2.6). To better understand transitions, scientists distinguish between the phases at which a transition occurs.

Roughly speaking, a transition can be divided into four phases (Ministerie van Infrastructuur en Waterstaat, 2022). In the first phase, the development, there is no visible change yet (Rotmans et al., 2001). However, small experiments are carried out locally, in which new, innovative ideas can be tested and improved (Rotmans, 2013). Then a tipping point takes place, where the process of change is catalysed and the first signs of changes in the system become manifest. In the acceleration phase, changes take place in all kinds of aspects of society, including institutional, cultural and economic, with the various developments influencing and reinforcing each other (Rotmans et al., 2001). In the third phase, the transition is also becoming increasingly large-scale, with changes spreading rapidly and becoming embedded. The fourth and final phase of the transition is characterized by stabilization and a decrease in the pace of change towards a new equilibrium and system (Rotmans, 2013).

During a transition, economic, cultural, technological and institutional aspects of the system change, among other things (Rotmans & Loorbach, 2009), whereby the change in each individual aspect is connected to and reinforced by the developments in other aspects. This makes the course of a transition unpredictable, erratic and subject to the unexpected consequences of feedback loops. Since many aspects of the system change, there are multiple barriers and facilitators to distinguish, which will be more elaborately discussed later (see 2.6).

Moreover, change involves moving from the safety of a well-known situation into more unfamiliar terrain, and therefore various individuals generally dislike change (Vennström & Eriksson, 2010). It is argued that changes in attitudes, behaviours and procedures are required in order to increase the chance of innovation, project success and improved end products (Mbachu and Nkado, 2006; Love et al., 2000; Dubois and Gadde, 2002).

Furthermore, according to Acemoglu et al. (2021), change is just as much a part of our experience as persistence is. What might persistence mean then one might ask? A more general perception of persistence is offered in works on path dependency and lock-in effect as discussed below.

2.5 Path Dependency and Lock-In Effect

The continued use of a product or practice based on historical preference or use is described as path dependency (Banton, 2021). An organization might be persistent with the preference to use a particular product or practice even if there are new, more efficient alternatives available. Path dependency frequently follows, when it is easier or more cost-effective to remain in an already set pathway than to construct a totally new one (Banton, 2021).

As Wiering, Liefferink, and Crabbé (2018) mentioned, “path dependency thus points to the tendency of persistence and self-reinforcement of paths and, by implication, the difficulty of changing a path once chosen” (p. 231). This then leads to the notion that the success of an innovation and therefore the adoption of a new technology depends on the path of its development, the so-called "path dependency", including the characteristics of the initial markets, institutional and regulatory factors that determine its launch and the expectations of social society (Foxon, 2002).

In the academic field, there is elaborated upon three degrees of path dependency. When the influence of some initial events on the ultimate result does not create any inefficiency, this is referred to as first-degree path dependence (Cecere et al., 2014). In the case of second-degree path dependence, there are practices that lead to undesirable outcomes that are not remediable, this occurs in a situation where, in the initial phases of the decisional process, there is insufficient information (Cecere et al., 2014). Ultimately, the third-degree path dependence indicates “a situation in which an inefficient outcome could have been avoided because of the existing better alternatives” (Cecere et al., 2014, p. 1042).

For the scope of this thesis, the research is only limited to the third-degree of path dependence, since there is evidence that there are alternative methods currently available that could substitute the use of nonhuman actors in the animal-based research and innovation industry, and therefore the inefficient outcome (i.e., the use of nonhuman actors) could be avoided.

The way in which new technologies develop is affected by the social, economic, and cultural environment in which they are created, and these technologies in turn also influence that environment (Rip and Kemp, 1998; Kemp, 2000). One key area of focus is how certain factors may benefit established technologies over new ones. Scholars such as Arthur (1994), argue that the more a technology is adopted, the more beneficial it becomes (a phenomenon known as "positive feedback"), leading to a "lock-in" effect where new, potentially better options are unable to gain traction. With growing returns to adoption, one pathway then turns into a routine because of self-reinforcing methods, and for this reason, the system locks itself

into a result that is not always superior to others, is not easily transformed, and cannot be anticipated in advance (Cecere et al., 2014).

The idea of lock-in is that technology and technological structures follow precise paths which are tough and expensive to escape (Perkins, 2003, as cited in Cecere et al., 2014). Even if advanced options are available, those technology and technological structures frequently live on for a long-lasting time.

Lock-in consequently refers to the result of the technological barriers and facilitators that systematically (dis)advantage certain developments and is therefore useful to look at to answer the questions in the context of the animal-based research and innovation industry in the Netherlands.

In this context, additionally, institutional path dependence plays an important role. Institutional change is heavily influenced by history as previous institutions play a significant role in determining the relative power dynamics between different groups and individuals. Additionally, changes to institutions can result in the redistribution of costs and benefits among different agents or groups (Brousseau et al., 2011). Therefore, when coalitions pushing for new regulations are unable to overcome or compensate for those who can inhibit or slow down the process of change, the current state of things may remain unchanged (Brousseau et al., 2011).

Existing technology, specifically technological systems, has seen a prolonged period of growth due to the phenomenon of increasing returns (Foxon, 2002). This growth is further reinforced by various institutional factors that also experience increasing returns (Foxon, 2002). The combination of these factors can lead to the formation of a Techno-Institutional Complex (Foxon, 2002), as can be observed in the animal-based research and innovation industry in the Netherlands. This complex can ultimately “lock out” the development of new, more sustainable technologies that have higher initial costs but have yet to experience cost savings from (1) economies of scale, (2) learning effects, (3) adaptive expectations and (4) network effects (Foxon, 2002).

As elaborated upon by Wiering, Liefferink, and Crabbé (2018) (1) economies of scale refer to the advantage of decreasing unit costs as output increases due to a significant initial investment in fixed costs; (2) learning effects refer to improved products or reduced costs through gained experience and knowledge as usage increases; (3) adaptive expectations refer to the expectations that adjust as the product becomes more prevalent, leading to increased belief in future market growth; (4) network effects refer to the benefits of working together with others who have taken similar actions.

2.6 Institutional, Technological and Normative Barriers and Facilitators

As mentioned before, there are multiple barriers and facilitators to distinguish when it comes to change. Change can occur due to for instance technological advancements, social pressure, economic development, regulatory forces, environmental issues, globalization, and conflicts (Robinson, 2008; Arranz et al., 2022; Seré et al., 2008; Presberger & Bernauer, 2023). Each of these forces constitutes different barriers and facilitators influencing them, which makes looking into them highly relevant to the scope of this thesis.

However, although there are numerous types of barriers and facilitators to be detected, since the transition towards non-animal-based research and innovation is mainly one of organisational, technological and societal influence, for the scope of this research we are diving into three types of barriers and facilitators, namely a) institutional, b) technological and c) normative barriers and facilitators .

By choosing these three pillars of change a structured framework is created, to be able to understand the different forces that influence the transition toward non-animal-based methods. It is not disregarded that there are other influences in this context, however, for the scope of this research it is useful to use the definitions of institutional, technological, and normative barriers and facilitators as a starting point. Adding to this, it is inherent in a theory that one can simply not perceive the complete representation of the subject of study and therefore the framework must be limited. Below, the reasoning why specifically the institutional, technological and normative barriers and facilitators as a framework were selected, is set forth.

First, recent research has progressively emphasised the role of broader institutional barriers and facilitators in influencing the transition toward more sustainable choices (Dai et al., 2015; Dubey et al., 2016; Levänen, 2015). Regarding institutional barriers and facilitators, institutions indicate “the rules of the game” in a certain society and refer to the humanly devised constraints that ultimately shape all human interaction (Vennström & Eriksson, 2010). These constraints can manifest as organizational forms, structural components, and rules (Douglass, 1990).

There has been great interest in examining how institutions evolve over time and how this creates certain barriers and facilitators to social change (Foxon, 2002). Institutions are generally understood as rules, norms and routines in a social environment (March & Olsen, 1989; North, 1990; Matten & Moon, 2008). Institutions can therefore include organisational forms, structural components and/or rules (North, 1990). Institutions can constitute power and control systems and typically replicate the dominant interests in society or in an organisation

(Vennström & Eriksson, 2010). The primary function of institutions in a society is to lessen uncertainty by organising a solid structure for human interaction (Vennström & Eriksson, 2010).

All the institutional forms mentioned above outline the institutional barriers and facilitators. Institutional facilitators are thus factors or forces that motivate or encourage change within an organization or institution. Institutional barriers, on the other hand, are factors that impede or prevent change from occurring. These can include organizational structures, policies, or situations that make it easier or more difficult to implement new ideas or technologies.

Moreover, institutional barriers and facilitators can be economic, political and social in nature (Lohse, 2019). Institutional barriers and facilitators, therefore, refer to the policies, procedures, or situations that ultimately systematically advantage or disadvantage certain people or developments (Ashcraft, 2009). Therefore, examining the various institutional barriers and facilitators in the transition to non-animal-based methods is relevant for this thesis. Since it can help to understand the factors that hinder or promote the transition to animal-free methods, which can contribute to the development of ethically sound alternatives. Additionally, targeted interventions can be developed to promote the implementation of animal-free methods, which can improve animal welfare.

Second, it is vital to consider that systemic changes rest on the development of new technology (Horbach, 2008), and thus, already established technological systems can be a substantial barrier to systemic change (Könnölä, et al., 2006). Additionally, technology plays a vital role in driving innovation and progress in various fields (Xiao D, Su J., 2022).

Technological barriers and facilitators can therefore be evident in a change process. Technologies interact to guide change along preferred channels and subsequently form barriers preventing the use of alternative methods (Berkhout, 2002). By understanding technological barriers and facilitators, researchers and policymakers can make targeted efforts to advance the development and implementation of cruelty-free technologies. By examining these aspects, policies and strategies can be developed to monitor and accelerate the transition to non-animal methods.

Additionally, targeted measures can be taken to provide the necessary infrastructure and support for the implementation of non-animal methods. Technological facilitators refer to the numerous technological opportunities that systematically advantage certain innovations. Technological barriers - in this context - refer to the various technological limitations that systematically disadvantage certain innovations.

Third, normative barriers can be apparent in change processes. Normative barriers refer to the various social norms, standards and even national legislation that systematically disadvantage certain developments or innovations, which are often regarded as safety barriers (Perrin, 2012). People and their respective attitudes comprise a vital barrier to change (Childerhouse et al., 2003; Post and Altman, 1994 as cited in Vennström & Eriksson, 2010). Normative barriers and facilitators to change refer to the social and cultural factors that influence the acceptance and implementation of change within an organization or society.

Normative barriers and facilitators reflect societal values and ethical beliefs (Sajjad, et al., 2020) in this case regarding the use of animal-based methods. By researching these aspects, one can better understand how norms, values and moral considerations influence the acceptance and implementation of non-animal methods. It helps to identify the normative aspects that play a role in decision-making and public opinion and can help facilitate positive change.

Furthermore, normative barriers and facilitators play a crucial role in influencing public acceptance and awareness (Nikitas, et al., 2018). Understanding the normative barriers and facilitators can thus help develop strategies to raise awareness, address misconceptions, and engage the public in discussions about non-animal-based methods.

Adding to this, normative barriers and facilitators play a role in shaping laws and regulations (Ranta, et al., 2018). Examining normative barriers and facilitators can as a result then help policymakers and regulators better understand what ethical and moral considerations should be considered when developing rules and regulations. This can lead to policy that supports and encourages the transition to non-animal methods.

2.7 Conceptual Model

From the research question; “*How do institutional, technological, and normative barriers and facilitators influence the current practices in the context of the animal-based research and innovation industry in the Netherlands, which is defined by path dependency and lock-in, in the transition towards non-animal-based methods?*” and the theoretical framework the following conceptual model, Figure 1, was created.

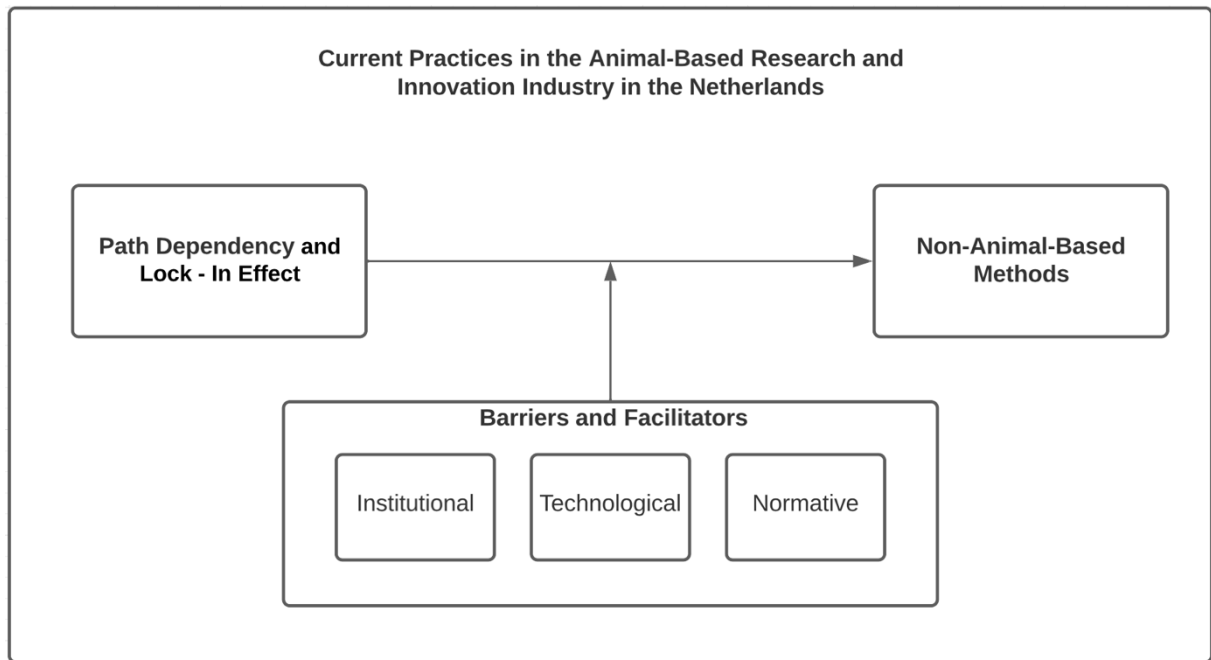


Figure 1. Conceptual Model

As shown in the conceptual model (figure 1), the transition occurring in the current practices, which is currently defined by path dependency and a sequential lock-in effect, towards non-animal-based methods is influenced by both barriers and facilitators as evident in the context of animal-based research and innovation industry in the Netherlands. As elaborated upon in the theoretical framework the barriers and facilitators in this case consist of institutional, technological and normative barriers and facilitators. From the conceptual model, it can be observed that these barriers and facilitators thus have an influence on the current practices, defined by path dependency and sequential lock-in, in the transition towards non-animal-based methods. It is therefore viable to study these concepts that ultimately influence and possibly obstruct the research and innovation industry in the Netherlands from moving towards non-animal-based methods.

2.8 Operationalisation

Resulting of the literature review and the conceptual model, for the operationalisation, the following figure was created.

Dimensions	Variables	Indicators
Actors	Non-Human	Laboratory Animals
	Human	The National Government Universities and Medical Schools Research Facilities Pharmaceutical Companies Laboratories Defence Establishments Commercial Facilities Non-Governmental Organisations
Barriers and Facilitators	Institutional	Policies
		Procedures
		Situations
	Technological	Technological Limitations and Advancements
Normative		Norms
		Standards
		National Legislation
Practices	Path Dependency	The continued use of a product or practice based on historical preference or use It is easier or more cost-effective to remain in an already set pathway
	Lock-In	Following path dependency the technologies and technological systems that are difficult and costly to escape

Figure 2. Operationalisation

From Figure 2. one can observe that each dimension has its variables that are to be detected by the consequential indicators in the data. By means of this operationalisation, the abstract concepts can be turned into measurable observations. In this way, one can systematically collect data on a phenomenon, such as for this thesis, that is not straightforwardly observable (Dovetail, 2023). It is important to operationalise the concepts since it allows one to clearly define and measure the variables of the study (Dovetail, 2023). This then helps to reduce any bias and subjectivity in the research (Dovetail, 2023).

3. Methodology

This chapter designates how the research was conducted. First, the research design, consisting of the research philosophy and strategy, is explained. Second, the research methods consisting of the data collection and analysis and last the assurance of the research validity and reliability will be described.

3.1 Research Design

3.1.1 Research Philosophy

A research philosophy can be defined as “a system of beliefs and assumptions about the development of knowledge” (Saunders et al., 2019). There are two pathways recognised for the research philosophy, namely epistemology and ontology. In the field of epistemology, one tries to create knowledge and values about what knowledge is and should be. Ontology, on the other hand, is about the nature of social entities, about what exists (Moon & Blackman, 2014). Within both research philosophies, there are continuums.

For ontology, this continuum is between realism and relativism. On the one hand, realism pertains that there is only one single reality that can be understood, experienced and studied as ‘real’, and this reality occurs independently of human experience (Moon & Blackman, 2014). On the other hand, relativism pertains that reality is composed within the human mind. Therefore, no single true world exists. Within this relativistic view, the reality is “relative according to each individual who experiences it at a given time and place” (Moon & Blackman, 2014, p, 1170).

For epistemology, this continuum is between subjectivism and objectivism. Subjectivism entails that “social reality is made from the perceptions and consequent actions of social actors” (Saunders et al, 2019, p. 137). Controversially, objectivism assumes that reality exists independent of the individual mind (Moon & Blackman, 2014). This research can be placed on the philosophy of ontology being on the relativistic side of the continuum. The aim of this study is to create a deeper understanding and broader knowledge on the topic of institutional, technological and normative barriers and facilitators as evident in the context of the research and innovation industry in the Netherlands in the transition towards non-animal-based methods.

Furthermore, this study is related to the philosophy of phenomenology. Phenomenology can be described as the study of structures of experiences, or consciousness (Smith, 2018). Literally, phenomenology means the study of “phenomena”; the appearances of things, or

things as they seem in our experience, or the ways in which we tend to experience things, and therefore the meanings things have in our experience (Smith, 2018). This research can be regarded as phenomenological since it is executed in order to create an understanding of the experiences of the Wageningen University & Research and experts in the field of the animal-based research and innovation industry in the Netherlands.

3.1.2 Research Strategy

A research strategy can be approached as a guideline for “the general plan of how the researcher will go about answering the research questions” (Saunders et al, 2009, p. 600). Considering that this research is meant to explore the concepts of path dependency, lock-in, and institutional, technological, and normative barriers and facilitators as detectible in the context of the research and innovation industry in the Netherlands regarding the transition towards non-animal-based methods, a qualitative method of research is the most suitable. With qualitative research one “studies things in their natural settings, attempting to make sense of, or interpret, phenomena in terms of the meanings that people bring to them” (Denzin & Lincoln, 1994).

Additionally, a qualitative study concerns gathering and decoding linguistic sources to make an assertion about a certain social phenomenon (Bleijenbergh, 2015). A quantitative research strategy would not suffice in this matter, since the aim is to qualitatively elaborate upon the influence of the institutional, technological, and normative barriers and facilitators, in the context of the animal-based research and innovation industry in the Netherlands, and upon the concepts of path dependency and sequential lock-in effect visible in the transition towards non-animal-based methods.

A more deductive approach is applied to conduct this research. With a deductive approach, one builds upon existing concepts and knowledge. The concept of institutional, technological and normative barriers and facilitators to change behaviour, path dependency and lock-in are already described by others. In this research, an in-depth study is conducted on how these concepts are observable in the context of the animal-based research and innovation industry in the Netherlands by means of qualitative data collection methods.

However, since the concepts of institutional, technological and normative barriers and facilitators to change behaviour have not been elaborated upon as extensively as the other concepts first an inductive analysis approach is applied, to explore the data and certain patterns, which is followed by a deductive approach. This approach is taken to ensure that no important results are missed by directly following a deductive approach.

3.2 Research Methods

3.2.1 Data Collection

This research entails a qualitative approach since the aim is to create a deeper understanding and broader knowledge on the topic of institutional, technological and normative barriers and facilitators, path dependency and lock-in evident in the context of the animal-based research and innovation industry in the Netherlands in the transition towards non-animal-based methods.

This research first involved a document analysis of the current academic literature on the topic of animal-based research, the current practices and developments in this field, and on the institutional, technological and normative barriers and facilitators, path dependence and lock-in effect as observed by other scholars.

In order to be able to collect sufficient data, such as documents and interviews, on their approach and the barriers and facilitators that can be detected in the Netherlands, Wageningen University & Research was chosen to conduct a case study. By means of a case study, it is possible to gain valuable insights into the thoughts, values, interpretations, opinions, attitudes, experiences and behaviour of the research objective (Swanborn, 2010). After much debate, this approach was taken since Wageningen University & Research showed the most viable data publicly available.

There are various case study research designs: single case versus multiple and holistic versus embedded (Stewart, 2001). A single case study design is best when a single research object/research event is used (Stewart, 2001). Contrary, a multiple case study design is used when there are various cases to study, several with comparable outcomes and others with dissimilar outcomes (Stewart, 2001). Additionally, a multiple-cases approach is appropriate when seeking to reproduce findings in a different setting (Stewart, 2001). For the purpose of this research, a single case design is most appropriate since there is only one object of research. Furthermore, the distinction between a holistic and embedded case study design. A holistic case study design has one unit of analysis for each case, while in an embedded case study, the case is split into multiple units of analysis (Yin, 2003). There are multiple units of analysis in this thesis: The Netherlands, Wageningen University and individuals (i.e., the experts) who are key players in both the Netherlands and Wageningen University. Thus, for the scope of this research, a single embedded case study design is the most appropriate.

Furthermore, to answer the research question in the context of the Netherlands, several experts in the field of animal-based research and innovation were interviewed, since expert interviews lend themselves to situations in which it might prove problematic or even impossible to gain access to a particular social field (Bogner, et al., 2009). This approach was applied after

multiple failed attempts to get in contact with several animal-based research institutions. Unfortunately, it was proven not possible to get in contact with such institutions, and therefore the initial plan, of interviewing both academics inside and outside the field of animal-based research and innovation, had to be adjusted.

Thus, for this research, the approach of a single embedded case study combined with expert interviews is suited best since the aim is to create a deeper understanding of the various barriers and facilitators visible in the context of the animal-based research and innovation industry in the Netherlands.

Within the case of Wageningen University, besides the document analysis, several experts were asked to participate in this study. However, again people were reluctant to reply, which resulted in only two academics that were willing to participate: Dr. Jurriaan Mes and Dr. Hans Bouwmeester.

Dr. Mes is a senior scientist at Wageningen, Food and Bio-based research, at Wageningen University & Research. Dr. Mes is performing experiments to analyse the health effects, but also the risk effects of foods. Based on lab experiments, animal trials and human intervention trials, Dr. Mes tries to substantiate what kind of food can possibly prevent diseases. Therefore, it was very relevant to speak to Dr. Mes.

Furthermore, Dr. Hans Bouwmeester is an associate professor at Wageningen University in the Department of Toxicology, with over 15 years of experience in the toxicological risk assessment of chemicals. Dr. Bouwmeester is “passionate about the development of novel and advanced in vitro models that emulate the key functionality of the human intestine and liver, and to use them for fundamental studies on the interaction of chemicals with cells” (Momentum, n.d.). It was highly relevant to interview Dr. Bouwmeester since he decided to no longer conduct animal-based experiments.

Asides from Wageningen University, as mentioned before, additional experts were asked to participate, in order to further strengthen the results. Unfortunately, due to a lack of response once more, only two additional experts were interviewed. First, an expert from Stichting Proefdiervrij; a Dutch foundation that is committed to making the use of laboratory animals unnecessary in scientific research and second, an expert from the Johns Hopkins Center for Alternatives to Animal Testing (CAAT). From Stichting Proefdiervrij Janneke den Besten - van Ravenswaaij was kindly willing to answer the questions. Den Besten - van Ravenswaaij is the science and communication officer at Proefdiervrij. From The Johns Hopkins Center for Alternatives to Animal Testing, Thomas Hartung, MD, PhD, Director of the Johns Hopkins Center for Alternatives to Animal Testing was more than willing to participate, to shed light on

his experience with the transition towards non-animal-based methods. Dr. Hartung “steers the revolution in toxicology to move away from 50+-year-old animal tests to organoid cultures and the use of artificial intelligence” (Johns Hopkins Bloomberg School of Public Health, n.d.) and was therefore asked to answer the questions on the barriers and facilitators visible in the transition towards non-animal-based methods.

The interviews were conducted by means of a two-step process. The first interviews were done by means of semi-structured interviews about the concepts of path dependency, lock-in, and institutional, technological and normative barriers, in order to be able to evaluate and compare the answers of the participants. These first set of semi-structured interviews were then followed by another set of semi-structured interviews following the answers to the first semi-structured interviews, focussing additionally on the institutional, technological and normative facilitators visible in the context of the research and innovation industry in the Netherlands, in order to create an in-depth understanding of the current situation to eventually answer the research questions. To obtain triangulation of the data collection, this study consisted of a mixed-methods approach through semi-structured interviews, and a document analysis of publicly available documents from the Wageningen University and policy reports, such as from the European Union and the Dutch Government. Noble and Heale (2019) explain that triangulation is “an effort to help explore and explain complex human behaviour using a variety of methods to offer a more balanced explanation to readers” (p.67).

3.2.1.1 Case Background

Wageningen University & Research is a collaboration between Wageningen University (WU) and Wageningen Research (WR) and carries out research into agriculture, nutrition, nature and the environment, partly by means of animal experiments (WUR Annual Report, 2021; Annual Report Animal Testing, 2022). In 2022 a total of 104,891 animal tests were carried out at Wageningen University & Research, which is an increase of 29% in contrast to 2021 (Annual Report Animal Testing, 2022). In comparison to the earlier mentioned average amount of 450,000 animal experiments per year in the Netherlands, this shows that Wageningen University & Research conducts almost a quarter of the total animal experiments. This demonstrates a substantial number of the total animal experiments conducted and is therefore valuable to use as an embedded case. Moreover, Wageningen University & Research is determined in its efforts to replace, reduce and refine animal testing (Annual Report Animal Testing, 2022), which is in line with the Dutch Government.

Furthermore, Wageningen University & Research is transparent regarding the animal tests they conduct (Annual Report Animal Testing, 2022). Therefore, a lot of information and publications are available to use for the scope of this research, making Wageningen University & Research useful and representative as an embedded case for the research and innovation industry in the Netherlands,

3.2.2 Data Analysis

The data is analysed by means of thematic analysis. Thematic analysis is a widely used qualitative data analysis approach (Javadi & Zarea, 2016). It is a method for “extraction of meanings and concepts from data and includes pinpointing, examining, and recording patterns or themes” (Javadi & Zarea, 2016, p. 34). Thematic analysis is suitable for data derived from interviews, literature, policy documents, and pictures or movies (Javadi & Zarea, 2016). Thematic analysis is used for the detection, evaluation and reporting of certain themes in data (Javadi & Zarea, 2016). This is a systematic iterative process.

In this study, the six phases of thematic analysis as defined by Braun & Clarke (2006) were used in order to analyse the data in a deductive, top-down matter, that is driven by the specific research questions (Maguire & Delahunt 2017). During the first phase, one must become very familiar with the data, e.g., through reading, and re-reading the transcripts of the interviews and literature. In the second phase, initial codes must be generated by means of open coding (Maguire & Delahunt 2017). In the third phase, themes will be explored, which is followed by the fourth phase of reviewing and the fifth phase of defining and naming the themes and the last phase of writing the results section. The coding has been executed with the use of ATLAS.ti in combination with a coding scheme, see Appendix 3, that was created beforehand. This resulted in a combination of an inductive and deductive method of analysis, developing a mixed methods analysis approach.

3.2.3 Validity and Reliability

There are two sorts of validity, one can discern between internal validity, which is related to the criteria of credibility, and external validity, which is related to the criteria of transferability (Guba & Lincoln, 1994). External validity suggests how accurately the results exemplify the phenomenon studied, establishing the generalisability of results (Yin, 1981). Reliability relates to the criteria of dependability (Guba & Lincoln, 1994). Since the data collection is by means of triangulation, this increases the reliability and both the internal and external validity of research findings. Triangulation, formed by combining methods in this study, can assist to ensure that biases are overcome that could potentially arise when one uses a single method of data collection (Noble & Heale, 2019).

To ensure that the results are reliable, a mixed methods approach was chosen for this study. By combining the case study and expert interviews with another set of expert interviews from outside of the case, the reliability of the results, whether they match or differ, will go up. Furthermore, to increase the validity and reliability, it must be recognised that multiple realities exist and therefore biases must be steered away from. During the coding process, it was made sure that no information was left behind to take up in the analysis based on biases therefore the results were checked both inductive and deductive by means of coding via ATLAS.ti and a beforehand created coding scheme.

Lastly, the participants' perspectives must be clearly and accurately presented (Noble & Smith, 2015). Likewise, any other researcher should be able to attain comparable or similar results (Noble & Smith, 2015). When any other researcher would replicate this research, with the same participants and methods, it can be said that the same results will be obtained since all information and data are processed accurately without bias of the researcher. Thus, in order to increase the validity and reliability of this study, a mixed-methods approach is applied, leading to triangulation.

4. Results and Discussion

This research involved a three-fold approach to answering the research question posed in the introductory chapter: *“How do institutional, technological, and normative barriers and facilitators influence the current practices in the context of the animal-based research and innovation industry in the Netherlands, which is defined by path dependency and lock-in, in the transition towards non-animal-based methods?”*

In this chapter, the outcomes originating from the document analysis and semi-structured interviews are explained and discussed in detail. By means of the data analysis, many beneficial insights have been discovered, revealing the impact of the institutional, technological, and normative barriers and facilitators on the current practices regarding animal-based research and innovation in the Netherlands, which is identified as path-dependent and locked-in, as the industry transitions towards non-animal-based methods. For the animal-based research and innovation industry in the Netherlands in particular, the results have enormous implications. The purpose of this chapter is to provide a comprehensive overview and discussion of the research results.

Divided into four sections, this chapter centres around the research aim and questions. The current practices in the Netherlands' animal-based research and innovation industry are put into context by the first section, which sheds light on Dutch and European policies regarding animal-based methods. The aim of the second section is to address the research's first and second sub-questions for which the animal-based research and innovation industry's current practices and developments were analysed by means of a document analysis and the interviewee's reflections. The subsequent section develops this in terms of the third sub-question of the concepts of path dependency and the lock-in effect regarding the transition towards non-animal-based research and innovation. The last section aims to elaborate on the influence of the institutional, technological, and normative barriers and facilitators that influence the current practices of the animal-based research and innovation industry to transition towards non-animal-based methods.

4.1 Dutch and European Policies Concerning Animal-Based Methods

Since 1986, the EU has had specific legislation on the use of animals for scientific purposes (European Commission, n.d.-a). On September 22, 2010, the EU adopted Directive 2010/63/EU, which updates and replaces Directive 86/609/EEC of 1986 on the protection of animals used for scientific purposes (European Commission, n.d.-a). The aim of the directive is to strengthen legislation and improve the welfare of animals that still need to be used, as well as firmly enshrine the principle of the three Rs, to replace, reduce and refine the use of animals in the legislation of EU (European Commission, n.d.-a).

Furthermore, the development, validation and implementation of alternative methods will be encouraged through actions such as the establishment of an EU reference laboratory for the validation of alternative methods, with the support of laboratories in the Member States, and encouraging Member States to promote alternative methods national level (European Commission, n.d.-c).

The term "alternatives" in this context includes all attempts, tests, methods, techniques, tools, strategies, and approaches etc. that contribute to the practical implementation of the "Three Rs" (European Commission, n.d.-b). That is obtaining the required information without the use of live animals; reducing the number of animals while obtaining the same level of information; improving the use of live animals to cause less pain, distress or suffering or to improve animal welfare (European Commission, n.d.-b). Alternative approaches offer opportunities to further develop the "Three R's", but equally aim to develop better and more predictive scientific tools to protect human and animal health and the environment (European Commission, n.d.-b).

In the Netherlands, the government, academia, businesses, and civil society organizations have been working together for years to promote the responsible use of animals in teaching and research (including scientific research) (Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2015). The Animal Experiments Act (WOD) came into force in the Netherlands in 1977. This law protects the welfare of laboratory animals, establishes frameworks that procedures must follow, and establishes experience requirements for those who work with laboratory animals (Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2015). On the 18th of December 2014, the WOD was revised. With this revision, the European Directive relating to animal procedures in research (2010/63/EU) was implemented within Dutch national legislation (Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2015). This legislation can be interpreted as such that the Dutch government has put in place a set of rules and regulations that govern the use of animals for scientific research purposes.

The legislation specifies which institutions are authorized to breed and raise animals, who is allowed to carry out animal experiments, the purposes for which such experiments can be carried out, and the conditions under which they can be performed. The legislation also outlines the responsibilities of the supervisory bodies that oversee animal experimentation, the procedure for obtaining a license for carrying out such experiments, and the requirements for training and further education of employees involved in the experiments (Animal Welfare Body Utrecht, z.d.). Overall, the influence of this legislation is that animal experiments in the Netherlands will be carried out under stricter regulations that ensure the welfare and ethical treatment of animals, therefore possibly driving the transition towards non-animal-based methods.

Furthermore, each license application for a research project involving animal testing must include a non-technical summary (NTS) written in Dutch (Animal Welfare Body Utrecht, z.d.). It sets out the objectives of the research and a justification for the use of animals, including the expected negative impacts on the animal's welfare and the application of the 3Rs, Replacement, Reduction and Refinement (Animal Welfare Body Utrecht, z.d.). The NTS must be written in simple wording so that it can be understood by a wide audience (Animal Welfare Body Utrecht, z.d.). The Central Authority of Scientific Procedures on Animals (CCD) will then publish the NTS without attribution of names (Animal Welfare Body Utrecht, z.d.). By doing so, the use of laboratory animals in the Netherlands can be made transparent without infringing on intellectual property rights or privacy (Animal Welfare Body Utrecht, z.d.). This legislation, therefore, underlines the importance of ethical considerations and transparency in animal-based research, and the steps that are taken to ensure that these principles are upheld in the Netherlands.

4.2 Current Practices and Developments

As mentioned before the Dutch government aims to establish the Netherlands as a pioneer in cruelty-free innovation by 2025 through a transition towards non-animal testing research (Ministerie van Landbouw, Natuur en Voedselkwaliteit, 2016). According to the Wageningen University & Research report (n.d.-c) on 'Food research without the use of animal tests' animal testing is often unreliable, costly, and raises ethical issues, which is why WUR has been devoted to developing alternative methods and models that simulate the behaviour of cells, organs, and the digestive system. By doing so, they aim to reduce the number of animal tests, make them less harsh by refining them, and ultimately replace them in food research. In the focus areas of biology, animal production, and life sciences research at Wageningen

University & Research, various research methods are employed. One such method includes the use of computer models for making calculations and forecasts. Additionally, laboratory experiments are a valuable tool in modelling processes or examining sub-processes within the human or animal body as stated in the WUR annual report (2020).

Despite the advancements in these research methods according to the WUR annual report (2020), there are still instances where animal experiments are necessary. As mentioned in their report 'Replace, reduce, and refine - WUR is reducing animal experiments' Wageningen University & Research (2020), is currently making diligent efforts to create a diverse collection of alternatives to the traditional method of animal testing. Wageningen University & Research (2020) recognizes the need for innovative solutions that not only provide accurate results but also align with ethical considerations for the treatment of animals. Through extensive research and development, the WUR is working to bring about a future where animal testing is no longer necessary, and instead, alternative methods that are both effective and humane can be utilized. The WUR has been engaged in a prolonged effort to develop alternatives to animal testing, specifically in bioassays. Bioassays, which involve infecting animals or administering substances to them to gauge their reactions, have long been used to determine the presence of pathogens in animal populations and hormone levels in blood. However, the WUR is exploring new laboratory techniques and DNA tests that could potentially provide more reliable results than traditional bioassays (Wageningen University & Research, 2020).

In addition to these advancements in testing methods, the WUR is also exploring the use of tissue cultures, organoids (miniature organs), and self-learning computer models that are based on vast amounts of data. These innovative approaches hold great promise as non-animal alternatives for bioassays, allowing for more accurate and ethical methods of testing.

The WUR's commitment to developing these alternatives underscores its dedication to finding innovative solutions that balance scientific progress with ethical considerations for the treatment of animals. Organisations such as Proefdiervrij do see very promising results when it comes to animal-free innovations.

In a lot of cases, researchers see even better results with human-oriented methods, for instance, researcher Berend van Meer, den Besten – van Ravenswaaij (Personal Communication, 2022) explains that he can predict side-effects of heart drugs better with a heart-on-a-chip, containing human heart cells. And there are even methods in which researchers try to recreate the entire system, like the Virtual Human Platform for Safety Assessment project den Besten – van Ravenswaaij (Personal Communication, 2022)

elaborates. In this project researchers are using human biology as a starting point, they are using a lot of existing clinical data from patients with specific diseases, and they use that as input for a computer model (den Besten – van Ravenswaaij, Personal Communication, 2022). Next to that, they are also studying the cells from patients in the lab, in the form of organs-on-chips, and they can add this data to the model. Additionally, they can also add data on medication compounds to the computer model, all this data can then be used to analyse diseases and potential drugs (den Besten – van Ravenswaaij, Personal Communication, 2022). Overall, the results show that there are several practices and developments currently happening in the research and innovation industry in the Netherlands.

4.3 Path Dependency and Lock-In

Animal experiments are a crucial aspect of education and research at Wageningen University & Research as stated in the WUR Animal Experimentation: Guidelines and Ambitions report (2022). Some of the animal experimentation at WUR is mandated by law, such as for the creation and oversight of vaccines and medications (Wageningen University & Research, 2022). The use of animals for research is a topic that can be complex and debatable, as acknowledged by this report. This report emphasizes on the need to balance the scientific value and the ethical concerns when conducting animal-based research. This report delves into the fact that even though the moral and ethical concerns surrounding animal testing are evident, it is worth noting that animal-based methods are still essential in scientific research and education. This view can be seen as 'positive feedback'. Chapter 2.2 of this thesis discusses the phenomenon of 'positive feedback,' which encourages the use of established models. As a result, a 'lock-in' effect often occurs, limiting the acceptance of potentially superior options. This brings to light the necessity of exploring new and alternative approaches.

However, due to the difficulty and duration of implementing new non-animal-based models in scientific research, Mes (Personal Communication, 2023) argues that the preference tends to be towards the use of known models that are already available and easy to handle due to previous experience. Likewise, Dr. Bouwmeester (Personal Communication, 2022) explained that when discussing newly launched projects, researchers will inevitably address the same obstacles that must be overcome, including institutional, regulatory, and additional barriers that also arise when interpreting animal-based data. However, for these new methods, one must consciously accept the uncertainty of the outcome, and it is proven to be easier to accept the uncertainty that arises with animal-based data since this has been done before

(Bouwmeester, Personal Communication, 2022). This implies that the current situation is path dependent since path dependency frequently follows when it is easier to stay in the already set pathway.

Moreover, while it is likely that we will replace the uncertainty of animal-based studies with a potentially known or unknown uncertainty in the in vitro world, Dr. Bouwmeester (Personal Communication, 2022) argues, it is uncertain if one can genuinely replace one type of uncertainty with another. It is deemed more comfortable to accept the uncertainty we are familiar with than to embrace a new form of uncertainty (Bouwmeester, Personal Communication, 2022). According to Dr. Bouwmeester (Personal Communication, 2022), this is the main obstacle that must be overcome; when will academia, industry, and regulators come together and agree to move forward? “We have been attempting to do this for 20 years or longer, but progress has been limited” (Bouwmeester, Personal Communication, 2022).

This use of established models, i.e., animal-based methods, based on historical preference or because it is simply easier to use can be directly observed as path dependency. The introduction of new (non-animal-based) models demands a stepwise approach to demonstrate the required capability, expertise, and consistency with previous research findings (Mes, Personal Communication, 2023). In some cases, researchers are denied approval to use a particular animal model in their facilities merely because it has not been previously used at that exact location, even though it has been used at other research facilities. Mes (Personal Communication, 2023) explains that this then forces the researchers to conduct a pilot trial, which may involve additional animals and quite often may not be financially viable. Consequently, the number of animal models available for research in a particular institute may be limited due to budget and time constraints.

Adding to this, micro-physiological systems and artificial intelligence show great promise in replacing animal-based methods for drug testing, according to Dr. Hartung (Personal Communication, 2023). However, the industry is currently hesitant to adopt these methods until they are proven to be effective, indicating an obvious degree of path dependency and lock-in. Due to historical preferences, the drug-testing industry appears to depend heavily on animal-based methods. Unfortunately, Dr. Hartung (Personal Communication, 2023) argues, this has resulted in slow-moving regulatory change. Nonetheless, it is becoming apparent that the industry is gradually distancing itself from animal-based testing, indicating that there is still an opportunity for progress. Likewise, Dr. Hartung suggests that policymakers and regulators have an important role to play in

facilitating this change and in breaking the path dependency and lock-in associated with animal-based testing methods.

Moreover, den Besten – van Ravenswaaij (Personal Communication, 2023) argues that when we look at the past up until now, there is a large knowledge base when it comes to animal testing. Animal testing is ingrained in the science culture, making it difficult to completely ban and switch to animal-free innovations, according to Den Besten – van Ravenswaaij (Personal Communication, 2023). Achieving a comparable level of knowledge with animal-based methods requires substantial investment in non-animal-based methods, meaning that sticking to the current path is more cost-effective and convenient. Animal research can also be quite expensive due to the need for long-term care for the subjects. Nevertheless, cost is only one of many factors involved in such studies. Animal testing can be quite costly, according to Den Besten – van Ravenswaaij (Personal Communication, 2023), animal tests can be expensive compared to some in vitro tests, although it ultimately depends on the method used for comparison.

Dr. Mes (Personal Communication, 2023) argues that it is proven easier and more cost-effective to remain in the current set pathway, that of using animal-based methods as a standard, but notes that the current situation simultaneously limits the range of research possibilities. If a researcher wants to move from in vitro experiments, for example, to animal or human trials, they may not be able to do so if the animal model is new and therefore unavailable, since then the researcher first must create a knowledge base based on more animal trials by conducting a pilot trial, which makes it even more expensive (Mes, Personal Communication, 2023). It even may be more difficult to proceed to human trials even if the animal model is available. Dr. Mes (Personal Communication, 2023) observed that some Dutch research groups, therefore, travel to other countries such as France or China to conduct their trials, this can raise ethical concerns about the treatment of animals in these locations, since research in the Netherlands, where animal welfare is a high priority, would be a better option.

Furthermore, on the Wageningen University news outlet 'Resource, WUR from within', Ramaker (2014) explained that alternatives that are scientifically superior must regularly wait extremely long for acceptance, showing that the current system, in which animal-based methods are the norm, is difficult to escape. Dr. Mes (Personal Communication, 2023) acknowledges that the use of more ethical research methods, e.g., non-animal-based methods, can be more expensive, causing challenges not only for applied or contract research but also for PhD students who may be working within the constraints of a limited budget. The

NWO, the Dutch research funding organization, grants a certain amount of funding to new researchers which restricts the number of experiments that can be conducted (Mes, Personal Communication, 2023). Dr. Mes (Personal Communication, 2023) argues that it can be difficult to obtain funding for their research if additional experiments need to be conducted before the real experiment can take place, the additional experiments may be considered too basic and have already been published by others. Consequently, this limits the range of research strategies that can be explored (Mes, Personal Communication, 2023). The technological system in place is therefore difficult and costly to escape, creating path dependency and consequently a lock-in effect. Even now when advanced alternatives are available, the current technological structures have been superior for a long time.

4.4 Institutional, Technological and Normative Barriers and Facilitators

Following extensive research and analysis, the findings indicate that there are various institutional, technological, and normative barriers and facilitators to be observed in the research and innovation industry in the Netherlands.

Although the prevailing regime of animal-based research and innovation primarily aims to preserve and enhance the functionality of this system, there are developments with other viewpoints that aspire to reform the system. The findings below show that the research and innovation sector in the Netherlands is undergoing a transition because it is undergoing a fundamental change and various coalitions of actors have different perspectives on reality and what the sector should or shouldn't do. Within a transition, there are numerous barriers and facilitators that could either accelerate the transition or hold it back. As discussed before, this happens in roughly four phases. The transition in the research and innovation industry in the Netherlands is currently in between the second and third phases, in which a tipping point takes place and the transition is accelerated. The earliest indications of systemic alterations appear since the process of change is catalysed by the facilitators. However, the barriers do slow down this process of change. These processes influence and reinforce one another. In the following subsections, each form of institutional, technological and normative barrier and facilitator detected will be elaborated on and their influence on the current practices is discussed.

4.4.1 The Influence of Institutional Barriers and Facilitators

According to the WUR Animal Experimentation: Guidelines and Ambitions Report (2022) the priority is always placed on adhering to the 3Rs principle in all animal experimentation research. This principle ensures that the research is ethically and humanely conducted, minimizing animal suffering, and maximizing welfare. Through this policy that could potentially act as an institutional facilitator, WUR makes investments in the development of alternative methods, seeking input and feedback from relevant stakeholders when feasible, therefore, positively influencing the current practices by promoting the development and use of alternative methods in animal-based research, which can ultimately lead to reduced animal suffering and improved animal welfare.

The impact and outcomes of these efforts are regularly monitored and reported, demonstrating WUR's commitment to the 3Rs. The 3Rs consist of three key elements 1) the replacement of laboratory animals with non-animal methods, with an emphasis on validating these methods, 2) a reduction in the number of animals used in laboratory research, 3) the refinement of methods for using laboratory animals to minimize stress and improve welfare (Wageningen University & Research, 2022). Regular monitoring and reporting of outcomes can help to identify and address any issues or concerns related to the use of these methods. Overall, this can contribute to a more ethical and sustainable approach to animal-based research and innovation.

In addition, one of the experts at Wageningen University mentioned that currently in the institutional environment, the policy is that one must write “an umbrella” (Mes, Personal Communication, 2022). To conduct an animal trial, one first must get permission for the general scope of the experiment you want to do, you have different work protocols that you then must provide. This policy follows a stepwise layer, in which one first must go to the internal commission of Wageningen University, then the national commission, and then they must go back to the internal commission before they are allowed to perform an animal-based trial (Mes, Personal Communication, 2022).

Furthermore, the commissions really look at the discomfort of the animals. And what researchers currently see is that these policies are becoming stricter than in the past, for instance, power calculations must be more precise than in the past, one must provide much more details. These policies all try to minimize the number of animal trials (Mes, Personal Communication, 2022). This umbrella policy could therefore be seen as a potential facilitator to change towards non-animal-based methods in the research and innovation industry. Since

this policy influences the current practices by making it harder to conduct animal-based research.

Furthermore, a policy of WUR states that prior to each practical session in education, a thorough evaluation is conducted to determine the necessity of using laboratory animals for educational purposes and to consider alternative options that may be available (Wageningen University & Research, 2022) which also facilitates the change towards non-animal-based methods by influencing the number of animals used in educational sessions.

However, in contrast to the policy of replacing, reducing, and refining, a policy in the annual report (2022) of the Wageningen University states that graduates may be required to conduct animal experiments as part of their work which could potentially act as an institutional barrier to change towards non-animal-based methods in the research and innovation industry since by this policy the current practices are influenced in a way that the use of non-animal-based methods is maintained by requiring students to conduct animal experiments.

Furthermore, according to Dr. Mes (Personal Communication, 2023), there is a new policy that forbids researchers from using other individuals' research in their own study, regardless of the similarity of the topic. If one intends to switch from one animal strain to another, a pilot trial, including additional animals, must be conducted to ensure that the same results can be obtained (Mes, Personal Communication, 2023). This policy can be observed as a barrier to transitioning towards non-animal-based methods since it requires additional animals and animal experiments instead of accepting the study that has already been conducted and therefore influencing the current path by maintaining it.

What is also interesting is that Dr. Mes (Personal Communication, 2022) mentioned that even though the WUR has set several policies to minimize the number of animals used for research, the food authorities still oblige them to conduct an animal trial on protein digestibility when one wants to launch a new protein into the market even though the new protein might not be as new. For instance, when they isolate the protein from a potato it is regarded as a novel food, and it is considered a new type of protein. In his professional opinion, in this case, animal trials are superfluous, there are good alternatives with in vitro models and human intervention trials (Mes, Personal Communication, 2022). The fact that the food authorities still require the researcher to conduct an animal trial, therefore, acts as an institutional barrier to change towards non-animal-based methods since it influences the current practices by maintaining it as it.

Likewise, Dr. Mes (Personal Communication, 2022) argues that one must follow a long way for a new method to get accepted. One must go through a whole ISO certification system. For instance, the trial should be performed in eight labs in five different countries, one must perform ring trials to get it accepted. “While for this type of analysis, I think it should not be that big of a deal to get an approval” (Mes, Personal Communication, 2022).

It has been an ongoing matter of debate whether animal testing should be utilized in developing drugs. Still, some researchers claim that the results of animal-based research do not reflect how these pharmaceuticals interact with human bodies. Despite this, policymakers continue to mandate animal trials as the go-to method for drug testing.

By helping identify safety concerns that would have otherwise gone undetected, animal testing has “made the world a safer place”, according to Dr. Hartung (Personal Communication, 2023). Though he recognizes that there are now more suitable drug testing tools available, he emphasizes that any changes to current practices must be approached with careful management and consideration. Transitioning away from animal testing poses the challenge of balancing international industry changes while handling potential liabilities and reputational risks, as explained by Dr. Hartung (Personal Communication, 2023).

It was found that the pursuit of alternative methods to animal testing is influenced by various factors, including both the personal motivations of the researchers and practical considerations such as the expenses associated with conducting animal experiments and the rigorous regulations in place (Wageningen University & Research, n.d.-a). While a research project may appear to be scientifically compelling, it may not be deemed ethically and morally acceptable. The independent review board responsible for evaluating all animal testing proposals carefully balances the significance of the research with the amount of suffering that will be inflicted upon the laboratory animals. In instances where the harm to the animals exceeds the potential benefits of the research, the researcher will not receive approval to proceed with the animal experiment (Wageningen University & Research, n.d.-a). This procedure to receive approval beforehand that must be followed as installed by Wageningen University could therefore potentially act as an institutional facilitator since by carefully considering the balance between the significance of the research and the potential harm imposed on laboratory animals, the review board helps safeguard that animal experiments are only conducted when necessary and that the animals involved are treated humanely.

Furthermore, it can be implicated that this evaluation process also highlights the need for alternative, non-animal-based research methods that can provide meaningful results without inflicting unnecessary harm on animals. Therefore, this procedure promotes more

responsible and ethical animal research practices, while also encouraging the development and adoption of non-animal-based methods in research.

On the other hand, according to Wageningen University & Research (n.d.-a), acquiring hands-on experience with live animals is an essential component of education for students pursuing a degree in animal science. It is deemed crucial for these students to have the opportunity to determine if they wish to work directly with animals and to acquire the necessary skills to do so. This can only be achieved through direct contact with animals and the conduct of animal testing, allowing students to fully understand the realities of working in this field. The provision of such opportunities is fundamental in providing a well-rounded education for future professionals in animal science (Wageningen University & Research, n.d.-a). This specific procedure at Wageningen University could potentially act as an institutional barrier to change towards non-animal-based methods, since it gives students the opportunity to conduct animal experiments instead of teaching them to search for alternatives, therefore, influencing the current practices.

Additionally, den Besten – van Ravenswaaij (Personal Communication, 2022) stated that there are procedures in place in the Netherlands to ensure the well-being of animals used in research, like the permit application procedure. For researchers at universities or medical centres to use animals in research projects, they need to get a permit. Researchers need to meet several requirements and go through several steps, to be able to conduct animal-based studies. They need to, for example, explain the research design and strategy, the number of animals used and the possibilities of replacement (of the animal experiments). These procedures stem from the 3Rs principle, which provides a framework for performing more humane animal research (den Besten – van Ravenswaaij, Personal Communication, 2022). This specific procedure in this institutional environment could be seen as a facilitator to change towards non-animal-based methods since it suggests that the Netherlands is already actively promoting the use of non-animal-based methods wherever possible. This is likely to have a positive influence on the transition towards non-animal-based methods. By emphasizing the importance of considering alternative methods and providing a framework for more humane animal research, the Netherlands is encouraging researchers to adopt more innovative and ethical approaches to their work.

However, as den Besten – van Ravenswaaij (Personal Communication, 2022) mentions these procedures do arise from the notion that we will be using animals in research projects in the long run. They are less focused on replacement and creating a scientific world in which we do not need animals to perform research studies (den Besten – van Ravenswaaij,

Personal Communication, 2022) and therefore simultaneously act as a barrier to transition towards non-animal-based methods by maintaining the current situation in which animal-based methods are the norm.

To stimulate the animal-free transition in scientific research, within the Dutch Research Agenda (NWA) 'Non-animal models: acceptance and implementation', three consortia, among which is one project of Wageningen University, will focus on the acceptance and implementation of animal-free models at a regulatory, scientific, and societal basis (NWO, 2022b). This specific institutional situation can be seen as a facilitator to transition towards non-animal-based methods.

Furthermore, on the Wageningen University news outlet 'Resource, WUR from within' it is mentioned that a PhD student of Wageningen University in late 1980 developed an alternative for a toxicity test on rabbits, which was only recently partially taken up by the international regulatory authorities. This situation clearly states how hard it is to try to get alternatives to animal testing accepted in European and international regulations. Alternatives that are often scientifically superior must wait a very long time for acceptance (Ramaker, 2014). This institutional situation, therefore, describes a barrier to the transition towards non-animal-based methods by making it hard to get new methods accepted and influencing the transition towards non-animal-based methods negatively. Nevertheless, this specific situation could also be seen as a facilitator since it was said that when the test would not be accepted, steps would be taken to get the European Parliament to examine internationally where the obstacles lie and how they can be removed (Ramaker, 2014). Resulting in potentially more knowledge on the several obstacles visible and how to overcome these, and therefore driving forward the change to non-animal-based methods.

Additionally, in situations where animal testing is mandated by law and the available alternatives are not yet dependable, the researchers at Wageningen University devote extra time to conducting preliminary research (Wageningen University & Research, n.d.-c). "We navigate this middle ground for research into the safety of products derived from genetically modified organisms, for example, or into the long-term effects of possible carcinogens" (Wageningen University & Research, n.d.-c). In the preliminary research phase, they establish the appropriate dosages of the substance that need to be examined and determine whether specific categories of animals, such as young, old, male or female, are required for testing (Wageningen University & Research, n.d.-c). By doing so, they can ensure that the number of animal tests is minimized (Wageningen University & Research, n.d.-c). This specific situation clearly describes an institutional facilitator to transition towards non-animal-based methods,

since it implies that researchers at Wageningen University are committed to minimizing animal testing in situations where it is mandated by law and there are no reliable alternatives available. They conduct preliminary research to establish appropriate dosages and determine which categories of animals are required for testing, in order to ensure that the number of animals used is minimized. This demonstrates their commitment to the ethical and responsible use of animals in research and working towards finding alternative methods.

Moreover, Dr. Hartung (Personal Communication, 2023) predicts that a transition in scientific methodology is underway, with increasing emphasis on finding effective alternatives to animal testing that are more human-specific, scalable, and efficient. This transition is complicated because of the widespread acceptance of animal testing in research, making it difficult to implement change but the transition is facilitated by increasing restrictions on animal testing and the desire to achieve better outcomes, which are getting more people to consider alternatives seriously.

Overall, this indicates that the use of animal testing in scientific research is a complex issue, involving both ethical and economic considerations, as well as traditional approaches to science. However, there is a growing movement towards seeking alternative methods, which may lead to a paradigm transition in the field.

4.4.2 The Influence of Technological Barriers and Facilitators

Next to institutional barriers and facilitators, technological opportunities and limitations can be visible in the transition towards non-animal-based methods in the context of the research and innovation industry in the Netherlands.

First and foremost, Wageningen University is ‘actively working on new technologies which can replace animal testing’ (Kleis, 2017). It was found that innovative methods, such as tissue culture or computer models, can substitute or minimize the need for animal testing. These alternatives have shown to be not only more cost-effective but also superior in some cases to conduct experiments on animals (Wageningen University & Research, n.d.-a).

Furthermore, novel technologies are emerging as viable options to eradicate animal testing for field studies. For instance, advanced DNA technology enables the gathering of extensive information on wild animals without harming them or requiring their capture and sedation for blood samples. This is because DNA analysis of animal faeces is a valuable source of information (Wageningen University & Research, n.d.-a). Moreover, there has been a systematic development of alternative methods for toxicity tests, hormone analyses, and other experiments, with a reduction in the use of laboratory animals for toxicological studies.

Tissue culture tests are now used as a pre-screening step before testing suspect batches on laboratory animals (Wageningen University & Research, n.d.-a).

Additionally, animal experiments have been replaced by experiments using tissue cultures and organoids, which are miniature organs grown from a tissue sample where all types of living cells function together. This approach has already been successfully employed with muscle, intestine, and liver tissue, allowing for a variety of experiments to be conducted (Wageningen University & Research, n.d.-a). All the technological opportunities potentially facilitate the transition towards non-animal-based methods, by focusing on replacing the use of animals in their field of studies with technological alternatives it influences the current practices to transition towards non-animal-based methods.

However, there are technological limitations, that make it more difficult to replace animal testing (den Besten – van Ravenswaaij, Personal Communication, 2022). Researchers often indicate that to study a specific disease, they need an entire system or body to study this disease. For example, den Besten – van Ravenswaaij (Personal Communication, 2022) explains, researchers need to see how multiple organs in the body are affected by a disease. Or they need to investigate how a type of medication is absorbed by multiple organs. And that is why they indicate that they need to study this in animals and that they cannot study this with an alternative. Most alternatives, like organoids or organs-on-chips, are focused on one specific organ within the body, and this makes it more difficult to use them to study the entire body (den Besten – van Ravenswaaij, Personal Communication, 2022).

Therefore, understanding and replicating the interactions and responses to substances between different systems of a whole animal has proven to be a complex task. As a result, it is unlikely that complete comprehension and successful replication of these interactions can be achieved through alternative strategies alone. In such situations, a comprehensive set of alternative tests and information from other sources would be necessary before completely abandoning animal use and resorting to total animal replacement (European Commission, z.d.-b).

Besides, it was argued by hundreds of scientists, amongst of which some from Wageningen University, that although there are several highly promising alternative methods being developed, conducting qualitatively comparable research without experimental animals is currently not feasible (NWO, 2022a). In the research and innovation industry in the Netherlands, we are used to considering animal-derived data but are we to say that we fully understand the complexity of what happens in their bodies? Dr. Bouwmeester (2022) would argue that that is not the case, “we simply observe, we put a chemical in an animal, and we

observe it, if the animal dies or if there is a liver effect for instance, and the causality, I think, is sometimes very poorly. However, we do have increased mechanistic information and understanding now more than ever because of in vitro studies”.

Adding to this Dr. Bouwmeester (Personal Communication, 2022) explained that even though there have been several developments in non-animal-based methods it currently does not fully capture the complexity of our bodies. For instance, it does not capture the distribution of the chemical taken orally, which fractions are ending up in the liver or in the kidney. “It is proven very difficult to capture with in vitro models, and that is why we need certain computer models to predict the distribution, the behaviour of the chemicals and the integration to eventually create a transition towards non-animal-based methods” (Bouwmeester, Personal Communication, 2022). This technological limitation therefore directly creates a technological opportunity to overcome the problem of capturing the complexity of our bodies as mentioned by Dr. Bouwmeester (Personal Communication, 2022).

Adding to this, Dr. Mes (Personal Communication, 2023) mentioned that with the technological opportunity of organoid research, one can focus on one type of response, but the communication between the different organs, the blood flow, and the balances, in the whole organism, long-term exposures, is all not possible by the current models. And he also cannot think of models that could do that in the future. Dr. Mes (Personal Communication, 2023) explains that there are ideas about putting organs on a chip, and the communication between those organs but “I do not see that this is a reflection of the whole organism, a whole animal or a whole human” (Mes, Personal Communication, 2023). So, it is really refining or reducing the animal trial by using those in vitro models, stepwise one can bring it back to some compounds with the highest potentials, and then test those with animal trials, since “it is very hard to go from in vitro models directly to humans” (Mes, Personal Communication, 2023).

Likewise, den Besten – van Ravenswaaij (Personal Communication, 2022) states that she sees a lot of developments when it comes to these alternatives. “Many researchers come to Proefdiervrij for funding, because they want to shy away from animal testing, and they want to work toward human-oriented research models” (den Besten – van Ravenswaaij, Personal Communication, 2022). The reason for this is that animals are not humans and there are a lot of limitations to using animal models to study human disease and to develop medication for humans.

Around 90% of drugs fail in clinical trials, because of drug toxicity or failure of efficacy in humans, even though drugs seem to work in animals, during preclinical trials, they

often do not work for humans (den Besten – van Ravenswaaij, Personal Communication, 2022). This not only costs animal lives and causes animals discomfort, pain, and stress, but it is also a huge waste of effort, money, and resources. And animal testing does not provide us with the answers that we need for a lot of diseases (den Besten – van Ravenswaaij, Personal Communication, 2022). Thus, one can certainly argue that there are still a lot of technological limitations visible that influence the transition towards non-animal-based methods.

As it turns out, there has been a change in focus regarding which obstacles lie ahead in terms of adopting new testing methods. While the technology used to be the main concern, Dr. Hartung (Personal Communication, 2023) has pointed out that there are some standout tech tools out there that make the switch achievable. Take for instance artificial intelligence and bio-engineered cell culture systems, both of which have been shown to be as good as, if not better than animal testing (Hartung, Personal Communication, 2023). In Dr. Hartung's expert opinion what we are currently facing is more of a change management challenge.

4.4.3 The Influence of Normative Barriers and Facilitators

Next to institutional barriers and facilitators, and technological opportunities and limitations, normative barriers and facilitators can be observed in the transition towards non-animal-based methods in the context of the research and innovation industry in the Netherlands.

In recent years, the norms surrounding the utilization of laboratory animals have become a topic of heightened scrutiny and criticism, with concerns arising from both societal and scientific perspectives (NWO, 2022b). These concerns revolve around several issues, such as the ethical considerations surrounding animal welfare and the translatability of research findings from animals to humans. As highlighted by NWO (2022b), these issues have contributed to the ongoing debate surrounding the use of laboratory animals in research.

There has been a notable decrease in the use of animals in research, which can be attributed, at least in part, to the growing societal and governmental pressures to reduce animal testing as mentioned in Resource, WUR from within, by Kleis (2017). Kleis (2017) argues that the government, in particular, has set an ambitious goal to make legally mandated safety and allergy tests for chemicals, new products, food ingredients, pesticides, and vaccinations entirely animal-free by 2025.

As a result, applications requesting the use of animals for experiments are being subject to increasingly rigorous scrutiny to ensure that all other alternative methods have been fully explored and exhausted (Kleis, 2017). This heightened scrutiny is part of a larger effort to balance the ethical considerations surrounding animal welfare with the scientific needs of

research. As explained in the article ‘Alternatives to animal testing’ by Wageningen University & Research (n.d.-a) performing an experiment involving animal-based-methods is only allowed if there are no alternatives available or if the test is legally compulsory, and to make critical decisions permission from the internal committee for animal experimentation is also required.

Furthermore, as stated in the annual report of 2020, at the Wageningen University the standard is to invest consistently for the implementation of the 3Rs (replacement, reduction, and refinement) in animal experimentation, and to promote the adoption of alternative testing methods within the European framework. In the annual report (2020) it is elaborated that the standard at WUR is, therefore, to proactively be involved in the creation and application of substitutes to animal testing, which may encompass the implementation of alternative research models or techniques that eliminate the requirement for animal testing (replacement), lower the number of test animals necessary (reduction), and/or minimize the distress inflicted upon animals by the research methods (refinement). Consequently, WUR is dedicated to promoting transparency concerning its animal experiments and engaging in mandatory social discussions on animal testing (Annual Report, 2020).

Likewise, Wageningen University and Research (n.d.-a) believes that animal testing has several disadvantages, for instance, it can cause suffering in animals and is relatively expensive. In addition, to determine the impact of a substance on humans, animal test results must be extrapolated to humans (Wageningen University & Research, n.d.-a). Research conducted by Wageningen University & Research (n.d.-a) indicates that in many cases, animal experimentation can be avoided, making the process of assessing food safety and nutrition more humane and cost-effective, while also providing more precise insights into how these substances impact humans.

Adding to this, as explained by Mes (Personal Communication, 2023), the social pressure to change the research industry helps to change the norms and standards at Wageningen University. Both internal, for instance from colleagues, and external pressure is making the researchers more sensitive to reducing the number of animal experiments conducted (Mes, Personal Communication, 2023). Likewise, to change the norms and standards, there is a lot of focus on animal-free innovations within the Dutch government (den Besten – van Ravenswaaij, Personal Communication, 2022). There is a governmental programme focussed specifically on animal-free innovations, called Transitie Proefdiervrije Innovaties. This initiative, as explained in the WUR eDepot, is working across diverse domains and disciplines, to prevent the unnecessary use of laboratory animals and achieve a

significant reduction in animal testing in the long term (Wageningen University & Research, n.d.-d).

All the above-mentioned changes in norms and standards can be seen as a normative facilitator to transition towards non-animal-based methods because the changing ethical concerns facilitate the transition towards non-animal-based methods. As societal norms and values shift towards greater concern for animal welfare, there is a growing push towards the use of non-animal methods.

In the field of biology, animal production, and life sciences research (which are the primary focus areas at WUR), various research methods are utilized. For instance, computer models are utilized to make calculations and forecasts, while laboratory experiments are employed to model processes or investigate sub-processes in the human or animal body. These methods have undergone significant advancements and are now yielding increasingly better results. However, despite these advances, there are still situations in which animal experiments remain the norm and, in some cases, animal experiments are a legal requirement, while in others, they are used for educational purposes, as outlined in the WUR annual report for 2021.

As mentioned before, in Dr. Hartung's opinion we are currently facing more of a change management challenge. Fine-tuning and continued advancement are key, as is redefining norms, standards, and legislation to make way for the implementation of these innovative techniques. Slowly but surely, the industry is inching its way towards non-animal-based methods, though Dr. Hartung (Personal Communication, 2023) highlights the pressure to quickly launch drugs as a major hurdle. Delays rake in millions of dollars by the day, and the industry is unenthusiastic about any changes that could put the registration process at risk. However, meeting the requisite standard has proven to be a 'tough nut to crack' amidst these obstacles (Hartung, Personal Communication, 2023).

Furthermore, Dr. Hartung remarks that drug development is an adaptable industry that readily embraces innovative technologies. Nevertheless, the FDA and other regulatory entities have a strong influence over which approaches are viable, and they can be unpredictable. Although animal-based methods have considerably decreased in usage for drug development, regulations continue to lag (Hartung, Personal Communication, 2023).

Adding to this, animal experimentation is still considered the primary method of research in the Netherlands and is held in high regard as the "gold standard" within the scientific community (den Besten – van Ravenswaaij, Personal Communication, 2022). den Besten – van Ravenswaaij, (Personal Communication, 2022) then explains that undoubtedly,

animal testing has contributed to a vast pool of knowledge. Nevertheless, there is a relatively limited knowledge base regarding animal-free, human-oriented methods, which poses a significant challenge for researchers who aspire to work on animal-free projects. With fewer resources to draw upon, these researchers face a higher barrier to entry in adopting alternative approaches (den Besten – van Ravenswaaij, Personal Communication, 2022). The fact that animal experiments are often still the norm and standard, even though, there are several developments and alternatives available could potentially be seen as a normative barrier to transition towards non-animal-based methods.

Next to norms and standards, (national) legislation is viewed as a normative facilitator and/or barrier. There has been an increase in legal and regulatory restrictions on the use of animals in scientific research, which has led to a greater focus on the development of alternative methods that can be used in place of animals. In the case of the research and innovation industry in the Netherlands, almost all regulation stems from European legislation as mentioned in section 4.1. A direct facilitator can be observed by the fact that according to the legislation set forth by the European Union, animal experimentation is strictly prohibited unless the experiment's societal significance surpasses the potential harm and suffering that the animals may endure (Wageningen University & Research, 2022).

However, this legislation can also be regarded as a normative barrier to transition towards non-animal-based methods since it states that “animal testing is still necessary or even mandatory in specific areas (for example vaccine development and monitoring) for scientific and/or social reasons” (Wageningen University & Research, 2022). It is proven to be extremely hard to get alternatives to animal testing accepted in European and international regulations (Ramaker, 2014).

Moreover, Dr. Bouwmeester (Personal Communication, 2022) explained that the regulation of chemicals, specifically within the European Chemical Agency (ECA) domain and the Food Standards Agency (FSA), as well as human drug development, all require safety assessments based on animal testing data. However, these organizations also include provisions that allow for alternative methods to be used instead of animal-based studies, if there is sufficient evidence or a strong indication that such alternatives would be more appropriate (Bouwmeester, Personal Communication, 2022).

Despite this allowance for discussion, in practice, it can be challenging to implement alternative methods. This area of regulation serves as both a facilitator for and a barrier to the adoption of non-animal-based research methods since it allows for alternatives but, in practice, the implementation of such alternatives can be hard for researchers.

Furthermore, the Dutch ‘Wet op Dierproeven’ which is aimed at limiting the harm done to animals in animal testing considers invertebrate animals as an exception to this law (den Besten – van Ravenswaaij, Personal Communication, 2023). Invertebrate animals do not have a nervous system, which implies that they do not possess the capacity to experience pain, and therefore are not subject to the same protections as other animals under animal welfare laws (den Besten – van Ravenswaaij, Personal Communication, 2023). Consequently, den Besten – van Ravenswaaij (Personal Communication, 2023) argues that there are no restrictions on the number of invertebrates that can be used in research, and no regulations governing their welfare.

However, recent research has indicated that for instance, the octopus, an invertebrate species, exhibits a high level of intelligence and appears to experience pain and suffering, leading some researchers to re-evaluate the need to protect certain invertebrates (den Besten – van Ravenswaaij, Personal Communication, 2023). This raises the question of whether other species of invertebrates may also be capable of experiencing suffering and distress. This exception to the animal welfare law can be seen as a normative barrier to transition towards non-animal-based methods since there is no regulation available for invertebrate animals, making the use of them easily accessible for researchers and potentially increasing the use of such kinds of animals in research.

Moreover, it can be concluded that while academia is willing to come up with alternatives to animal trials, regulations and legislation often prescribe the use of animal testing. According to Dr. Hartung (Personal Communication, 2023) the reliance on animal testing is institutional and not due to cost factors, as the animal testing industry generates trillions of dollars. The prescriptive nature of legislation creates a conservative interpretation of regulations, making it difficult to promote change to alternative approaches. The most effective approach would be to identify the hazard or problem and leave it to the agency to provide current advice on the best approach.

As discussed by Dr. Hartung (Personal Communication, 2023), the practice of animal testing for chemical safety assessment has its disadvantages and limitations. International agreements also uphold the stance taken by the US FDA on this matter. Nevertheless, it is crucial to emphasize that the alteration of regulations should be in the hands of professionals rather than politicians, as the latter approach would not adhere to a scientific and effectual method (Hartung, Personal Communication, 2023). He argues that animal testing should no longer be the main option and other methods should fill the gap rather quickly.

A few explanations as to why animal testing is not ideal were given by Dr. Hartung. Firstly, tests on animals are not always reproducible, so the outcomes are never certain. Secondly, animals and humans differ greatly physiologically, making animal testing irrelevant to humans. Using animal models to predict how humans respond to chemicals is not an effective method as explained by Dr. Hartung (Personal Communication, 2023) who highlights that humans have a unique physiological makeup and cannot simply be compared to rats.

Another normative barrier visible is the fact that as stated in the WUR annual report (2020) as a standard a great part of the research in animal health, food safety and environmental pollution is statutory research that is commissioned by the Dutch government. Animal experiments at WUR are therefore often carried out as part of statutory tasks. “Wageningen Research conducts these experiments on behalf of the government, mostly to fulfil the obligations of international treaties in the context of public and animal health” (Wageningen University & Research, n.d.-a).

On the other hand, according to the WUR animal experimentation: guidelines and ambitions report (2022), WUR is devoted to stimulating the acceptance of alternative testing in international research practice. This applies to statutory tasks for which strictly prescribed, internationally agreed methods have been set forth. In such cases, according to Wageningen University & Research (2022), the evidence, that shows that alternative methods are sound or even better than existing animal-based methods, must be accepted as part of a complex political-legal process. To be able to do this, specialised expertise on political and legal issues is required, and this expertise does not come with every alternative methods researcher (Wageningen University & Research, 2022).

Therefore, WUR bundles the initiatives “aimed at gaining approval of alternative methods and uses specialised expertise to achieve this aim” (Wageningen University & Research, 2022). The fact that WUR is challenging this standard of statutory tasks could be observed as a normative facilitator to transition towards non-animal-based methods.

In the interview, Mes (Personal Communication, 2022) explained that he believes that there is a perception that conducting alternatives to animal trials involves the completion of checklists, where failure to satisfy certain requirements can result in a roadblock to acceptance, even for products that are highly sustainable.

Furthermore, sustainability benefits are not factored into the evaluation process, which focuses exclusively on assessing risks (Mes, Personal Communication, 2022). This narrow approach is driven by a desire to avoid any negative consequences, such as allergies, which could lead to legal liabilities. However, in the case of such incidents, it is possible to take

corrective action, such as introducing new food labelling, rather than simply avoiding non-animal-based testing due to fears (Mes, Personal Communication, 2022).

Moreover, the regulations on animal trials differ among various countries in Europe, making animal experimentation a debatable topic. Many PhD students who want to carry out animal trials often choose to conduct them elsewhere in Europe due to the stricter regulations on animal experimentation that can be found within The Netherlands. It is believed by Dr. Hartung (Personal Communication, 2023) that these regulations in the Netherlands are a positive thing since it makes it more difficult for researchers to perform animal experiments which means they must provide stronger justifications and pay greater amounts for animal care.

In comparison to Europe, the US conducts a higher volume of animal testing, perhaps due to its ease and affordability. Dr. Hartung (Personal Communication, 2023) highlights the importance of minimizing animal experimentation without cause and promoting alternative methods to society. In his opinion, the importance of animal experiments to science is overstated. Lastly, he suggests that the pursuit of alternatives is hindered by the narrow definition of what is considered an "alternative" method - only regulatory tests are replaced.

5. Conclusion

This research aimed to gain valuable insights into the roles of institutional, technological, and normative barriers and facilitators that are detectable in the context of animal-based research and innovation industry in the Netherlands, which is constrained by path dependence and lock-in, in their transition towards non-animal-based methods. Based on a qualitative analysis of the various available (policy) documents and semi-structured interviews, it can be derived that a multitude of practices and developments are currently being implemented in the animal-based research and innovation sector in the Netherlands, such as the use of computer models for making calculations and forecasts, the use of tissue cultures, organoids (miniature organs), and self-learning computer models that are based on vast amounts of data.

Due to the high cost and the difficulty of replacing animal-based experiments, these practices have become locked in and dependent on the previous path taken. Despite the availability of advanced alternatives mentioned above, the current (animal-based) technological structures have remained superior for an extended period.

The dominant regime of animal-based research and innovation is mainly aimed at maintaining and improving the functioning of this system, however, there are currently groups emerging with different perceptions that aim to transform the system. As observable from the results, there is a transition progressing within the research and innovation industry in the Netherlands since it is currently going through a fundamental change where different coalitions of actors have distinctive interpretations of reality and what the industry should or should not do. It is apparent that the stage of this transition is between the tipping point and the acceleration phase since the first signs of changes in the system are visible. For instance, many researchers aim to reduce the number of animal tests, make them less harsh by refining them, and try to ultimately replace them. However, path dependency mechanisms are impeding this change. To better understand how this transition works this research focussed on the influence of institutional, technological, and normative barriers and facilitators on this transition detectable in the research and innovation industry.

First, institutional barriers and facilitators, such as adherence to the 3Rs principle, influence these current practices and developments in animal-based research, prioritizing minimizing animal suffering and maximizing animal welfare. Universities have policies that make it harder to conduct animal-based research and evaluate the necessity of using laboratory animals for educational purposes. However, policies that require graduates to conduct animal experiments and oblige researchers to conduct animal trials for food authorities act as barriers to transitioning towards non-animal-based methods.

Second, technological opportunities facilitate the transition towards non-animal-based methods. Innovative methods such as tissue culture, computer models, and advanced DNA technology can substitute or minimize the need for animal testing. However, there are technological limitations, and complete comprehension and successful replication of interactions between different systems of a whole animal have proven to be a complex task. Qualitatively comparable research without experimental animals is currently not feasible, according to many scientists. Nonetheless, non-animal-based methods have increased our mechanistic information and understanding, and they can be used in combination with animal studies to refine or reduce animal trials.

Third, it can be concluded that there is growing societal and governmental pressure to reduce animal testing in research due to ethical concerns and translatability issues. Factors such as the personal motivations of researchers and expenses associated with conducting animal experiments also influence the pursuit of alternative methods. This has led to a decrease in animal testing and increased scrutiny of applications requesting animal experiments. Wageningen University is proactively involved in implementing the 3Rs and promoting transparency in animal experimentation. The changing ethical concerns act as a normative facilitator for a transition towards non-animal-based methods. In the scientific community, animal experimentation remains the ‘gold standard’ even though computer models and laboratory experiments have shown promise in producing improved outcomes. Despite this, researchers face a higher barrier to entry into non-animal-based methods of research because of a lack of relevant knowledgebase.

Overall these institutional, technological and normative barriers and facilitators, therefore, influence the current state of friction either by preserving the current system or by creating a tipping point. Since the facilitators catalyse the process of change, the early signs of systemic changes become apparent. The barriers do, however, impede this transformational process. These processes of catalysing and impeding have an impact on and reinforce one another continuously.

The institutional, technological, and normative barriers and facilitators in the animal-based research and innovation industry in the Netherlands are, therefore, interconnected, presenting a complex and challenging landscape. The interlinkages between these barriers and facilitators highlight their mutual influence. For instance, on one hand, institutional support and funding for non-animal-based research are linked to technological opportunities, as they can facilitate the development of innovative tools and methods to reduce animal suffering and improve animal welfare.

On the other hand, technological limitations, such as data analysis techniques can act as barriers to the implementation of non-animal-based approaches. Regulations and legislation that prescribe animal-based research, can create barriers and reluctance to invest in alternative methods. Moreover, normative facilitators, influenced by ethical concerns and public opposition, can shape institutional regulations and standards, and vice versa, leading to stricter regulations or limitations in research practices.

Other examples of interlinkages between barriers and facilitators include the personal motivations of researchers which facilitates normative changes, as societal values shift towards greater concern for animal welfare, prompting a push for non-animal-based methods and corresponding technological developments. However, normative barriers may arise if there is resistance or scepticism towards adopting these animal friendly alternatives. Stricter institutional regulations and guidelines may be necessary as public opinion evolves, emphasizing the balance between research significance and harm inflicted on animals.

The emphasis on the 3Rs principle and the framework for more humane animal research encourage researchers to adopt innovative and ethical approaches, influencing norms, standards, and technological opportunities. Projects focusing on animal-free models and the Netherlands' institutional situation contribute to normative barriers and facilitators, as they influence norms, standards, and legislation. Technological opportunities to replace animal use facilitate the transition towards non-animal-based methods and necessitate updated institutional policies and training programs. The norms surrounding laboratory animal utilization face scrutiny and can be challenged by technological advancements that enhance translatability. The current standard of animal-based research presents a normative barrier but also opens technological opportunities for researchers to develop new alternatives.

Overall, these interlinkages demonstrate that institutional, technological and normative factors influence and shape one another, presenting a complex interplay within the research and innovation industry in the Netherlands.

5.1 Implications for Broader Scholarship and Practice

This thesis was written to shed light on the institutional, technological, and normative barriers and facilitators as observable in the research and innovation industry in the Netherlands. This thesis could therefore be of use to all stakeholders in this industry such as the Ministry of Agriculture, Nature and Food Quality, organizations conducting animal-based research and organisations such as Proefdiervrij to inspire them and other scholars to build on this thesis and develop further research.

Additionally, the Dutch government has the aim to establish the Netherlands as a pioneer in cruelty-free innovation by 2025 through a transition towards non-animal testing research. This, therefore, increases the pressure to adopt non-animal-based methods and requires action and knowledge of the institutional, technological, and normative barriers and facilitators in the research and innovation industry in the Netherlands.

This thesis was written to contribute to academic knowledge in this field and aid in the transition towards the usage of non-animal-based methods and the welfare of animals used in research.

Furthermore, this thesis bridged a gap in the academic literature on animal welfare in the field of animal-based research and innovation as well as enriches the already existing academic knowledge on the topic of animal welfare and animal-based research and innovation since scientific research contesting the current behaviour of the research and innovation industry in the Netherlands towards nonhuman actors and their welfare has not been conducted before in this specific field. By filling this gap, this thesis can contribute to a more comprehensive understanding of the (influence of the) institutional, technological, and normative barriers and facilitators as observable in the research and innovation industry in the Netherlands and thus provide a foundation for further research.

Another implication for broader scholarship is that this thesis presents new data that is obtained from interviews with several experts in this field that can be used to advance knowledge and understanding and can furthermore be used to develop further research.

As mentioned before, scientists, entrepreneurs, and social organizations perceive various opportunities for research and testing without animals. However, as observable from the result section a lot of alternatives are lacking in practice due to various reasons. This thesis can therefore prove to be highly valuable for practical purposes as it specifies valuable insights into institutional, technological and normative barriers and facilitators and their influence on the current practices that can serve as a foundation for various stakeholders, such as the Ministry of Agriculture, Nature and Food Quality, organizations conducting animal-

based research and organisations such as Proefdiervrij to build upon and hopefully, one day overcome the barriers and enhance the facilitators in the transition towards non-animal-based methods. The information presented in this thesis, therefore, serves as a valuable resource for these multiple parties to leverage and further develop upon.

Additionally, certain barriers usually hinder change, identifying them can help to apply fitting strategies to overcome them, thus helping to better incorporate the change at hand. Therefore, the identification of the barriers and facilitators in this thesis could help practitioners to seek out what barriers lie ahead and create an appropriate strategy to overcome them and use the facilitators as a catalysator to enhance the transition towards non-animal-based methods.

Thus, as mentioned before policies and support structures can be created, from this thesis as a starting point, to promote the adoption of non-animal-based methods and drive scientific progress when the barriers and facilitators are distinguished. Adding to this, policymakers can as a result of the information available in this thesis take more effective measures to reduce the use of animal testing and promote alternatives.

Last, this thesis could be used to create awareness as well. Creating awareness among the public on feasible non-animal-based methods and the barriers that keep away the transition towards these methods could potentially create pressure from society in order to catalyse action taken in the research and innovation industry in the Netherlands

5.2 Recommendations for Further Research

Based on the findings of this study, there are several areas that require further exploration to advance our understanding of the influence of the institutional, technological, and normative barriers and facilitators as observable in the research and innovation industry in the Netherlands in the transition towards non-animal-based methods. This chapter provides a set of recommendations for future research that can address the limitations and gaps identified in this study. These recommendations aim to contribute to the existing body of knowledge in the field and offer practical insights for policymakers, practitioners, and researchers interested in the institutional, technological, and normative barriers and facilitators visible in the transition towards non-animal-based methods. The following sections outline the specific areas for further investigation and provide justification for their inclusion.

The identification of the barriers and facilitators and their influence as done in this research can be seen as a first step towards non-animal-based research and innovation. Conducting a follow-up study focussing on how to overcome the barriers and enhance the

facilitators in order to enable the transition towards non-animal-based research and innovation could be highly interesting for both scholars and practitioners in the field.

Second, it would be highly interesting to conduct further research on this topic by collecting data from those who are currently working with animal-based methods in order to gain valuable insights into their point of view on this matter. Conducting a study on a larger scale, perhaps even incorporating international perspectives, could yield even more intriguing results with broader applications and as a result, the findings could be much more generalizable.

An additional study in the future, beyond 2025 since the Netherlands aims to become a forerunner in animal-free testing methods, would also be an interesting approach to analysing the evolution of these practices over time. This could offer valuable insights by comparing the results obtained from both studies.

Additionally, conducting an expanded mixed-methods study could be very interesting to gain a deeper understanding of the influence of institutional, technological, and normative barriers and facilitators on the animal-based research and innovation industry in the Netherlands. The study could then, for instance, use a strategy that combines both qualitative and quantitative data, resulting in a more comprehensive understanding of the influence.

5.3 Limitations of the Study

Qualitative research is a type of research that aims to explore and understand the subjective experiences, opinions, and meanings that people attach to certain phenomena. Although qualitative research can provide rich and nuanced insights into a topic, it also has some limitations that should be considered.

First and foremost, the fact that the course of this study had to change multiple times due to a repetitive lack of response from several actors in the research and innovation industry in the Netherlands, most importantly from those who are currently working with animal-based methods could be considered as a limitation. Due to this, the problem of bias and subjectivity arose in the analysis, since I was only able to interview professors from Wageningen University, a campaigner from Stichting Proefdiervrij and the director of the CAAT. Which are all actively participating in phasing out the use of animals in research and innovation. This entails that the result section of this thesis is not based on answers from actors who are currently intensively working with animal-based methods and can therefore be slightly biased and subjective.

Second, the limitation of limited generalizability, since qualitative research typically focuses on a specific group or population, the findings may not be generalizable to other populations or contexts, in this case, the generalizability of the data obtained from the case study on the Wageningen University is limited. The fact that Wageningen University is quite progressive in its approach makes the results of this thesis not fully generalizable for the rest of the Netherlands. However, since Wageningen University operates under a contract with the Dutch government, one can suspect that most findings will be generalizable.

Third, since this research involves data collection methods such as document analysis and expert interviews it is more difficult to replicate the study precisely and this would be a time-consuming process. And last, this thesis does not provide quantifiable data that can be analysed statistically, making it difficult to compare and contrast findings across studies.

Adding to this, one must understand that the theory on which this thesis is based could not comprehend all types of barriers and facilitators that potentially influence the transition towards non-animal-based methods. It is therefore important to be critical of the results and not disregard the fact that this thesis was only able to shed light on a part of a whole complex landscape.

Furthermore, the process of this thesis was not an easy one, to say the least. While at the beginning I was extremely enthusiastic to start once I found a topic and an internship, I was passionate about, this changed after being disregarded by numerous individuals that I tried contacting in order to collect information and data. Even this process shows the rigidity of this industry and the unwillingness to speak to someone with questions about why it is not changing, and the influence of barriers and facilitators shows the path-dependent and locked-in culture, in my opinion. Luckily, I was able to find a different approach, after multiple failed attempts, and found a spark of motivation, that worked for me.

6. References

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Appendix 1. List of interviewees

Name	Date
Jurriaan Mes	14-09-2022
Hans Bouwmeester	22-09-2022
Janneke den Besten-van Ravenswaaij (per email)	01-10-2023
Jurriaan Mes	02-02-2023
Janneke den Besten-van Ravenswaaij	14-02-2023
Thomas Hartung	28-02-2023

Appendix 2. Interview guide

Interview Guide First interview

Regular questions

- Who are you and what do you do?
- Could you tell me something about your specialization in the field of animal-based methods?

Questions to answer the research question

- What type of policies do you see in place when it comes to animal-based research and innovation in the Netherlands?
- Could these policies potentially act as barriers to transition towards non-animal-based methods? If so, how?
- What are the procedures that you see visible in the context of animal-based research and innovation in the Netherlands?
- Could these procedures potentially act as barriers to transition towards non-animal-based methods? If so, how?
- Could you describe any situations in the current institutional environment that could potentially act as barriers to transition towards non-animal-based methods?
- Do you see technological limitations that hinder a transition towards non-animal-based methods in the context of the animal-based research and innovation industry in the Netherlands?
- In the current situation in which animal-based research and innovation occurs in the Netherlands, do you see any norms or standards that could potentially act as barriers to transition towards non-animal-based methods?
- Is there any national legislation that you could describe as a barrier to transition towards non-animal-based methods?
- Do you, as an expert, see any other barriers to transition towards non-animal-based methods?

Interview Guide

Follow-up interview

In our earlier interview, I asked you about barriers to transitioning towards non-animal-based methods, in order to elaborate more in my thesis I am now also looking at facilitators that could potentially transition the current situation.

- Do you want to add anything to the previous answers?
- Could these policies potentially act as facilitators to transition towards non-animal-based methods? If so, how?
- What are the procedures that you see visible in the context of animal-based research and innovation in the Netherlands?
- Could these procedures potentially act as facilitators and/or barriers to transition towards non- animal-based methods? If so, how?
- Could you describe any situations in the current institutional environment that could potentially act as a facilitator to transition towards non-animal-based methods? If so, how do these act as facilitators?
- Do you see technological opportunities that benefit a transition towards non-animal-based methods in the context of the animal-based research and innovation industry in the Netherlands? If so, how do these benefit a transition?
- In the current situation in which animal-based research and innovation occurs in the Netherlands, do you see any norms that could potentially act as facilitators to transition towards non-animal-based methods? If so, how do these act as facilitators?
- In the current situation in which animal-based research and innovation occurs in the Netherlands, do you see any standards that could potentially act as facilitators to transition towards non-animal-based methods? If so, how do these act as facilitators?
- Is there any national legislation that you could describe as a facilitator to transition towards non-animal-based methods? If so, how do these act as facilitators?
- Do you believe there are any other facilitators visible?
- In the current situation in which animal-based research and innovation occurs in the Netherlands, do you see continued use of animal-based research based on historical preference or use? If so, how?
- In the current situation in which animal-based research and innovation occurs in the Netherlands, do you believe it is easier or more cost-effective to remain in an already set pathway? If so, why?

If answered yes to the above question(s)

- In the current situation in which animal-based research and innovation occurs in the Netherlands, do you believe that the technologies and technological systems are difficult and costly to escape? If so, why?

Appendix 3. Document Analysis (Coding) Scheme

Document Analysis Scheme

Document:

Date:

Data Extract	Code	Theme
	Policies	Institutional Barriers
		Institutional Facilitators
	Procedures	Institutional Barriers
		Institutional Facilitators
	Situations	Institutional Barriers
		Institutional Facilitators
	Technological limitations	Technological Barriers
	Technological opportunities	Technological Facilitators
	Norms	Normative Barriers
		Normative Facilitators
	Standards	Normative Barriers
		Normative Facilitators
	National Legislation	Normative Barriers
		Normative Facilitators
	Continued use of practice based on historical preference	Path Dependency
	Easier or more cost-effective to remain as is	Path Dependency
	Systems that are difficult and costly to escape	Lock-In