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The conceptual analysis and ethical consideration of the benefit concepts in the harm-benefit analysis

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(Jürgen Thanner)

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Table of contents:

| | |
|---|-----|
| Plagiatserklärung | I |
| Note of thanks | II |
| Table of contents: | III |
| 1. Abstract (Deutsch) | 1 |
| 2. Abstract (English) | 3 |
| 3. Introduction | 5 |
| 4. Definitions | 15 |
| 4.1. Brønstad benefit classification system..... | 16 |
| 4.2. Harm-benefit analysis..... | 17 |
| 4.3. Peter Singer's preference utilitarianism | 19 |
| 4.4. Tom Regan's animal rights view | 23 |
| 5. Aim of the master's thesis | 27 |
| 6. Methodology | 28 |
| 7. Results | 35 |
| 7.1. Concrete benefits from animal testing | 36 |
| 7.2. Findings in a quantitative perspective..... | 40 |
| 7.3. Practical benefits versus knowledge benefits | 42 |
| 7.4. Operational aspects of benefit concepts for the justification of animal experiments | 44 |
| 7.4.1. Modulating factors of benefit concepts..... | 46 |
| 7.5. The weighting of knowledge, practical, and secondary benefits in terms of justification in animal research | 50 |
| 7.5.1. Justification by Preference Utilitarianism..... | 51 |
| 7.5.1.1. Knowledge benefit | 51 |
| 7.5.1.2. Practical benefit | 53 |
| 7.5.1.3. Secondary benefit..... | 55 |
| 7.5.1.4. Results..... | 56 |
| 7.5.2. Justification by Animal Rights View | 58 |
| 7.5.2.1. Knowledge benefit | 58 |
| 7.5.2.2. Practical benefit | 60 |
| 7.5.2.3. Secondary benefit..... | 61 |
| 7.5.2.4. Results..... | 62 |
| 8. Answer to the research question | 64 |
| 9. Summary | 67 |

| | | |
|------------|--|-----------|
| 10. | Discussion | 69 |
| 11. | Implication for scientific research | 76 |
| 12. | Abbreviations..... | 77 |
| 13. | References | 78 |
| 14. | Figures | 90 |
| 15. | Tables | 91 |

1. Abstract (Deutsch)

In der Vergangenheit ist eine Vielzahl an Versuchstieren geopfert worden, damit das menschliche Wissen vermehrt wird sowie die menschliche Praxis einfacher und effizienter gestaltet werden kann. Allerdings ist in der Bevölkerung eine zunehmende Sensibilisierung gegenüber Tieren in wissenschaftlichen Experimenten bemerkbar. Die gesetzlichen Rahmenbedingungen besagen, dass Forscher*innen eine Schaden-Nutzen Abwägung durchführen müssen, um Versuche mit Tieren durchführen zu dürfen. 2010 implementierte die Europäische Union die EU-Richtlinie 2010/63/EU, damit in den ethischen Kommissionen eine Schaden-Nutzen Analyse (SNA), für die Projektevaluierung von Tierversuchen, durchgeführt werden muss. Seit dem Inkrafttreten der EU-Richtlinie 2010/63/EU müssen die zuständigen Behörden in den jeweiligen europäischen Mitgliedsstaaten eine Projektbeurteilung durchführen, die als einen wesentlichen Bestandteil die SNA umfasst, bevor Tierversuche initiiert werden dürfen. Auf der einen Seite der SNA müssen die Schäden für die Tiere in Form von Leiden, Schmerzen und Ängsten evaluiert und einbezogen werden. Auf der anderen Seite der SNA befinden sich die potenziellen Nutzen für Menschen, Tiere oder die Umwelt. Hierbei erhebt sich die Frage, ob das Wissen oder der praktische Nutzen als Rechtfertigung für die Schäden an Tieren in wissenschaftlichen Experimenten herangezogen werden soll. Die Ambivalenz zwischen dem Wissenszugewinn und dem praktischen Nutzen, kann am Beispiel der Masernimpfung nachvollziehbar illustriert werden. Heutzutage werden in den Medien oft neue Masernfälle und Masernausbrüche aus verschiedenen Ländern berichtet, weshalb dieses Thema noch immer eine hohe Aktualität innerhalb der Gesellschaft besitzt. Die Debatte der Masernimpfung unterstreicht die Tatsache, dass der praktische Nutzen des Impfens von bestimmten Menschengruppen nicht anerkannt werden muss und somit über der wissenschaftlichen Erkenntnis eingereiht wird. Doch sind potenzielle praktische Nutzen ohne gesichertes Wissen realisierbar? Diese Masterarbeit beschäftigt sich mit der Frage nach einem genaueren Verständnis des Nutzens in der SNA für die Projektevaluierung von Tierversuchen. Des Weiteren stellt sich die Frage nach einer ethischen Gewichtung der jeweiligen Nutzen für die finale Entscheidung der Projektevaluierung von Tierversuchen. Aus diesem Grund besteht das primäre Anliegen der Masterarbeit darin, dass die Konzeptualisierung des Nutzens in der Tierforschung genauer unter die Lupe genommen wird. Hierbei wird eine retrospektive

Analyse der Publikationen in der medizinischen Datenbank „PubMed“ durchgeführt, um das aktuelle Verständnis des Nutzens, innerhalb der Schaden-Nutzen Abwägung, in der Tierversuchsdebatte zu erhalten. Das sekundäre Anliegen der Masterarbeit besteht darin, dass die Konzeptualisierung des Nutzens durch den Tierrechtsansatz von Tom Regan und dem Präferenzutilitarismus von Peter Singer durchleuchtet wird. Infolgedessen werden der Tierrechtsansatz und der Präferenzutilitarismus als ethische Rechtfertigungen für die jeweiligen Nutzenkonzepte in der SNA herangezogen, um Argumente zu entwickeln, ob ein Tierprojekt oder -experiment ethisch gerechtfertigt ist. Die Intention besteht darin, zu klären, inwiefern der Tierrechtsansatz und der Präferenzutilitarismus Argumente für oder gegen die Entscheidung von Projekten mit Tierversuchen liefern können, wenn auf praktischen Nutzen und Nutzen im Sinne eines Zugewinns von Wissen abgehoben wird. Die Argumente können die endgültige Entscheidung der zuständigen Behörden bestätigen, ob ein Tierversuch durchgeführt werden soll. Aus diesem Grund führt der Inhalt der Masterarbeit zu folgender Forschungsfrage: Kann es gerechtfertigt sein, in der Schaden-Nutzen-Analyse, im Rahmen der Tierrechtssicht bzw. des Präferenzutilitarismus, den praktischen Nutzen über Wissenszugewinne zu stellen?

2. Abstract (English)

In the past, a large number of experimental animals have been sacrificed to increase human knowledge in medical research and to make human practice simpler and more efficient. However, there is a growing awareness of animals needs among the population, which is why researchers need a reasonable justification for their animal experiments. In 2010, the European Union implemented the EU Directive 2010/63/EU to require a harm-benefit analysis (HBA) to be carried out in the ethical commissions for the project evaluation of animal experiments. Since this EU Directive 2010/63/EU, the competent authorities in the respective European Member States must conduct the HBA before the animal experiment can be performed. On the one hand, the competent authorities must evaluate and assess the expected harms, in terms of suffering, pain, and distress, on animals within the research project. On the other hand, the HBA, an assessment of the potential benefits for humans, animals, or the environment must be performed and weighed against the expected harms on animals. The question arises as to whether knowledge or practical benefits can be used as a justification for animal suffering in scientific experiments. The ambivalence of the knowledge benefits and the practical benefits can be illustrated with the measles vaccination example. Nowadays, the media often reports new cases of measles and measles outbreaks from different countries, which is why this topic still has a high level of topicality within society. The debate on measles vaccination highlights the fact that practical benefits of vaccination do not need to be accepted by certain groups of people and are thus ranked above scientific knowledge. Are potential practical benefits feasible without reliable knowledge? This master's thesis deals with the question of a more accurate understanding of the benefit concepts in the HBA for the project evaluation of animal experiments. In addition to that, the second purpose of the master thesis elaborates the question of an ethical weighting of the respective benefits for the final decision of the project evaluation of animal experiments. For this reason, the primary concern of the master's thesis is that the conceptualization of the benefits of animal research should be examined more precisely. A retrospective analysis of the publications in the medical database "PubMed" is performed to obtain the current understanding of the benefits, within the HBA, in the animal research debate. The secondary purpose of the master's thesis is that the conceptualization of the benefits is investigated by Tom Regan's animal rights view and Peter Singer's preference utilitarianism. Consequently,

the animal rights view and preference utilitarianism are used as ethical justifications for the respective benefit concepts in the HBA to develop arguments whether an animal project or experiment is ethically justified. The created arguments can confirm the final decision of the competent authorities whether an animal experiment can be carried out. For this reason, the content of the master's thesis leads to the following research question: Can it be justified to prioritize practical benefits over knowledge gains in the harm-benefit analysis within the framework of the animal rights view or preference utilitarianism?

3. Introduction

In this section of the master's thesis, the current subject of the research will be presented, and the research question will be depicted. For this reason, the legal aspect of the harm-benefit analysis (HBA) in the European Union will be firstly described. At next, past balancing possibilities (Porter's scoring system **(1)** and Stafleu's checklist **(2)**) of the HBA will be delineated. Furthermore, a summary of the harm dimension will be outlined. Moreover, a current overview of the number of animal experiments in Austria will be demonstrated. Next, the measles example will be used to show the ambivalence between the knowledge and the practical benefits. Finally, the role of the research question will be accentuated and in addition to that, the relevance in the debate on animal experiments will be highlighted.

Nationally and internationally the increasing interest in regulatory guidelines for the use of animals in scientific research is growing. The problem at hand is that it is enormous tension and difficulty in how to achieve a satisfactory justification, in terms of the incommensurability between the interests of animals and the benefits of human beings.**(3)** For this reason, the European Commission, the OIE, and the CIOMS-ICLAS established guidelines to secure adequate consideration of animals in research. The first Animal Ethics Commission was developed in Sweden in 1979.**(4)** Today, all European Member States must follow EU Directive 2010/63/EU and corresponding national law to get a project approved and this includes the HBA. The project assessment must contain in particular of the following: "the HBA of the project, to assess whether the harm to the animals in terms of suffering, pain, and distress, is justified by the expected outcome taking into account ethical considerations, and may ultimately benefit human beings, animals, or the environment" **(3, 5)**. This definition demonstrates that EU Directive 2010/63/EU comprises several normative components that define those conditions as acceptable for an animal experiment to be carried out reasonably. All animals that must be classified as worthy of protection (life and embryo vertebrates and cephalopods) are defined.**(5)** In addition, precise definitions of what can be considered as a project, breeder, supplier, etc. are sought. Moreover, the tolerated killing methods and allowed stun options are defined.**(5, 6)**

In the past, many approaches have been described as to how the HBA should be carried out **(1, 2, 4, 6–8)**. Typically, this was accompanied by outlining inherent weaknesses and problems. The advantages of the HBA are that it raises awareness

of harm reduction, that the application of the 3R principles is no longer enough, and that the accounting for harm and benefits should be transparent, consistent, and comprehensible. Several approaches have been developed that include checklists, score-systems, algorithms, graphical presentations, and generic processes.(6, 8, 9)

Porter devised an ethical tool that addresses the issue of whether and when an animal experiment can be considered morally feasible in a catalogue of scored criteria.(1) Therefore, it is essential to determine an ethical ideal. The aim of this ideal is to establish a reasonable standard that can be used as a basis for justification. After defining the philosophical ideal, Porter developed a scoring system with the view of achieving a concrete practical application. The scoring system consists of six categories for the pain dimension, two categories for assessing the quality and urgency of the experiment, and one category for the choice of animal species. Points can be awarded between one and five in each category. The benefit of the scoring system is that it strives for pragmatic decision-making processes that are as objective and efficient as possible for researchers. The difficulty of scoring systems is that the cut-off value should be kept low, adapted with increasing time, and unaffected by manipulations. Moreover, Porter's scoring system is not applicable in all areas of research, as the relevance is discussed differently by the population and is therefore tolerated differently. Besides, objectivity is only feigned, since moral positioning is already revealed in the determination of the moral ideal.(1)

Stafleu devised a system that combines all identified moral aspects into one checklist and addresses specific moral assumptions and decisions.(2) The factors described in the checklist help to evaluate the fundamental considerations for the respective justification. The established checklist includes eight steps, each of which contains important moral implications. The penultimate step calculates the harm score of the animals. Finally, the ethical acceptability of the animal experiment is assessed. Each step generates a certain number of points, which is why the same criticism as the scoring system is applicable that arithmetic tools are inappropriate for moral decision-making processes, although a comprehensible and transparent judgment can be made.(2)

So far, the current understanding of the HBA has been set out and its importance for the project evaluation of animal experiments has been emphasized. In addition, the difficulty of weighing harms and benefits has been explained and two approaches, plus their strengths and weaknesses, for project evaluations have been

demonstrated. The aforementioned aspects of the ethical decision-making process in the HBA show that the various methods (questionnaire, scoring system, or checklists) have not produced definitive solutions. In the following, the harm dimension will be outlined in more detail.

The concept of 3R principles was first introduced by Russel and Burch (10), which resulted in a reduction, replacement, and refinement of animal experiments.(10, 11) Both a reduction in the number of animals and the use of alternatives for animal experiments, such as *in vitro* experiments and minimization of pain and distress in an experiment, are necessary preconditions for a positive ethics assessment.(6) Tannenbaum emphasized the aspect that the well-being of an animal should not only be judged by the pain level (12), but also the intrinsic value (13) and self-realization (13) of a living being play an important role, which is why the focus should not only be on the harm dimension.(14, 15) Another tool for the harm dimension is the 5-freedom concept (16–18). This concept includes the freedom from hunger and thirst, the freedom from discomfort, the freedom from pain, injury, or disease, the freedom from fear and distress, and the freedom to guarantee the expression of normal behavior.(19) Every freedom dimension is assigned to a grading system of five levels and a specific justification is formulated for each grading tier. However, the problem is that research cannot always meet all the dimensions of freedom, as – for instance – cancer research deliberately aims at introducing a genetic defect in the animal genome to generate a corresponding disease.(19, 20) The factors animal species (1, 2, 5, 7, 21–23), number of animals (1, 2, 5, 22, 23), sentience and consciousness (5, 24), animal status (2), duration of the experiment (1, 2, 22), end point of the experiment, genetic manipulation (23, 25), competence of the personnel (2, 21–23), animal husbandry (including discomfort, pain, injury, fear, anxiety, and severity) (1, 4, 5, 7, 21–24, 26–28), and animal welfare capability play a decisive role for the ethical project evaluation.(6)

The purpose of the paragraph above was to show that the harm dimension has been conceptualized and dealt with several analytical tools (3R principles, 5-freedom concept, "animal welfare harms", "animal right harms", and "quality harms") which are used in the assessment of animal experiments in project evaluation to increase the welfare of animals. The definition of the harm dimension in the HBA is substantial because the term harm must be clarified to perform the balancing process with the potential benefits of animal projects. The relevance of the harm dimension for the research question is that the ethical considerations in the assessment of animal

projects must consider both the potential benefits and the expected harms of animals. In addition to that, it is crucial that benefit concepts can be balanced and weighed against the harm to animals in terms of suffering, pain, and fear **(5)**.

In the following, an overview of animal experiments in Austria will be shown.

Many experimental animals are used every year and for decades to generate useable knowledge for medical therapies. According to the scientific community, animal testing is seen as an important necessity to gain useful knowledge for medical practice.**(29)** Pursuant to paragraph 22(4) of the Animal Experiments Act 2012 (TVG 2012), BGBl. I No. 114/2012, idgF., the responsible Austrian authorities must transmit the data on the previous calendar year to the Federal Minister for Education, Science, and Research for publication in the form of common statistics on the Internet without personal reference. In 2018, 237,727 animals were recorded in the respective databases in Austria.**(30)** In 2019, approximately 246,300 animals were used for testing procedures in Austria.**(31)**.

According to the Austrian Directive 2012 (§ 5 TVG 2012) **(32)** for permitted animal testing purposes, the following purposes are listed: 1. basic research 2. translational or applied research 3. development and manufacture as well as quality, efficacy, and safety testing of medicinal products, food, feed, and other substances or products, if this is necessary to achieve the objectives set out in Z 2 4. protection of the natural environment in the interests of human or animal health or welfare 5. research on species conservation 6. education at universities or training to acquire, maintain or improving professional skills 7. forensic investigations.**(32, 33)**

This master thesis focuses on knowledge (= basic research) for medical practice (e.g. therapies, medical drugs) and the application possibilities for patients (= translational research) that can be generated from animal projects. The question here is whether the knowledge gained in research is sufficient to justify animal experiments or a certain practical benefit must be achieved. Furthermore, it is necessary to find out if the practical benefit is more decisive than the benefit of knowledge or vice versa, to approve animal experiments. For this reason, the paragraph showed that a vast and constantly increasing number of animals is needed in scientific research projects to generate knowledge and practical benefits in medical practice. In the following, the next paragraph presents a practical benefit that has been made possible through animal research in the 19th and 20th centuries **(34)**. This practical benefit is to vaccinate people against infectious diseases. The example of

measles vaccination demonstrates that the knowledge and practical benefits influence each other in reality. For this reason, the upcoming paragraph underlines the importance of the perspective on knowledge and practical benefits.

Infectious diseases depict an extraordinary cause of the enormous mortality rates in human history. Life expectancy after birth in developing countries is growing due to the reduction and control of infectious diseases.**(35)** Over time, more and more knowledge was accumulated about the life cycles of the pathogens responsible for the mortality rates. Smallpox, cholera, or measles are illustrative examples, which have had a decisive impact on the demographic change of the countries concerned. Vaccination was a powerful achievement that saved many lives by controlling and preventing threatening infectious diseases. There are still fierce debates in the media world about whether vaccination is a blessing. In professional circles, the effectiveness and necessity of vaccination can be answered unequivocally with a 'Yes'.**(35)** This position is due to the fact that, for example, the measles vaccination provides lifelong protection against the wild type, that the live vaccine for measles is an attenuated virus and thus a weakened disease discourse is expectable, the spread of the measles virus in society is reduced or can be stopped, thereby ensuring public health and the possible side effects of vaccination are less dangerous than the natural infection with the measles virus.**(36–38)**

In the following, I will demonstrate the argument of the scientific community and also present the counter-argument of the anti-vaccination view. In addition to that, I am going to expound on the historical development of the measles vaccination and describe the current measles situation. The rationale for the research question is that the knowledge benefit concept and practical benefit do not have to be accepted by all groups of people. The gain in knowledge from animal projects is objective as exact as possible and subject to biological laws of nature (interaction between pathogen and immune system, antibody production, etc.). Furthermore, the practical benefit should be tolerated and used by the people. One possible intention of animal projects is that many people should take advantage of them. However, research objectives must be adapted to people's needs so that research intentions do not come to anything, and the ethical consideration of animal projects can be reasonably reflected.

One counter-argument of the anti-vaccination activists is that they claim that people were also contracted the measles virus before the 1960s. Measles is presented as a normal and harmless infectious disease to encourage the anti-vaccination

program.(39) However, there is some bias in this counter-argument. For example, the "reporting bias" states that an act of remembering a specific event may be different between those who had a disease and those without the disease.(40, 41) Patients with a severe clinical history of measles are in favor of vaccination, whereas those with a mild clinical history are more likely to oppose vaccination. Another bias is the "survivor bias". The survivor bias describes the fact that in public debates, there are mainly those people who have survived the measles disease. Due to the measles malady, many death cases can no longer express their opinion in public.(40, 41) Ultimately, the "selection bias" demonstrates that the few anti-vaccination activists receive a disproportionate overrepresentation in the public debate, although there is a consensus among medical professionals that measles is a highly infectious and potentially fatal disease.(42–44)

One argument for the measles vaccination displays the person's self-protection, which is not limited to one season, as in the case of influenza. It is, of course, necessary for each person to have an individual benefit-risk assessment, in which vaccination protection and vaccination risks are weighed against each other. Subsequently, the measles vaccination protects other people as well. Therefore, all people who cannot be vaccinated (e.g. vaccination intolerance, immunosuppression during chemotherapy, or age) will be safeguarded. The collective aim of vaccination in society is herd immunity or disease eradication. For example, for herd immunity, the vaccination rates of 83-94% would prevent the spread of measles, even if measles cases happen in isolated cases.(45) Marckmann (46) speaks of herd immunity as a public good because it is characterized by the following characteristics: Large sections of the population must cooperate to achieve this good. Here, the individual benefit is subsumed to the collective benefit. Moreover, no one is excluded from herd immunity. Furthermore, a reduction in measles infection cases will affect the health system and reduce economic damage by reducing the number of working absenteeism.(46)

Measles represents a contagious infectious disease caused by the measles virus that can spread from one human to another human through coughing or sneezing of infected persons. Typically, the following symptoms can occur due to a measles infection: cough, Koplik's sport (white spots in the oral mucosa), inflamed eyes, maculopapular exanthema, and fever.(36, 47) In addition to that, serious complications such as middle ear infection (7%), diarrhea (8%), pneumonia, or the life-threatening condition subacute sclerosing panencephalitis. Intriguingly, the measles virus can only

infect humans and does not concern any other animal species. Unfortunately, there is no specific treatment against the measles virus infection which is why this problem (serious complication and no causal treatment option) can be solved by preventive measles vaccination. The only way to manage measles infection is supportive care such as oral rehydration solution, healthy food, and medical drugs to control the fever.**(36, 47)**

Therefore, measles vaccination was introduced in the early 1960s and recommended in 1976 in all healthy children between 6-15 months, as part of the MMR (measles, mumps, and rubella) vaccination program. After 12 months of vaccination, 95% of vaccinated children had a protective antibody titer against the measles virus. However, two doses are needed to provide adequate protection and prevent further disease transmission.**(48)** Between 1982-1984, a case-control study of 536 deaths and 1072 sex and age-matched patients was performed. Measles vaccination was associated with a 36% (95% confidence interval 21%-48%) proportionate reduction in the overall rate of death and a 57% (95% confidence interval 43%-67%) reduction in the rate of deaths directly attributed to measles or ascribed to diarrhea, respiratory illness, or malnutrition.**(49)** Another study collected longitudinal data from 8135 vaccinated and 8135 randomized matched non-vaccinated subjects observed up to 60 months. This study took place in the Matlab area of Bangladesh. A 40% risk reduction in vaccinated patients compared to non-vaccinated patients was found.**(50)** So far, there is no causal treatment against the measles virus malady. Subsequently, measles disease management occurs through supportive care (oral rehydration solution, healthy food, and medical drugs to control the fever).**(36, 47)** Measles virus elimination has been able to reduce the death rates of 1-4-year-olds from 90/1000 deaths to 50-40/1000 deaths (in terms of live births) in Bangladesh.**(49, 50)** Between 1987 and 1998, children vaccinated and unvaccinated in Colorado (between 3-18 years old) were retrospectively evaluated to see if there was a difference in incidence rates of measles. It was found that unvaccinated children were 22 times more likely to develop measles than vaccinated children.**(51)**

To sum up, it must be emphasized that measles is a seriously severe disease that has no causal therapy option, might lead to fatal complications (pneumonia or subacute sclerosing panencephalitis), and has primarily an increased mortality rate in infancy and childhood. The measles vaccination makes it possible to develop immune protection at a young age by generating protective antibodies against the measles

virus. The impact of the protective measles virus vaccination on the reduction of death rates and measles cases has already been shown in various studies, such as in Bangladesh **(49, 50)**, Colorado **(51)**, Turkey **(52)**, or the Netherlands **(53)**.

For this reason, the following paragraph is intended to show that the side effect rate of measles vaccination is in a low single-digit range and that the absence of protective antibodies from the measles vaccination can again lead to an increase in measles cases. This illustrates the practical benefit of the measles vaccination for individual and collective protection against measles disease.

According to the World Health Organization, the number of measles deaths diminished by 79% from approximately 651 600 to 134 200 cases per year.**(54)** Furthermore, immunization of measles vaccination can increase life expectancy by achieving positive indirect effects on other causes of death (e.g. diarrhea avoidance after measles vaccination).**(49)** Measles is a highly contagious viral infection and can have serious complications such as pneumonia or brain inflammation. Other secondary vaccination reactions include local pain, inflammation, fever, nausea, or vomiting. In a few cases, parotitis, febrile convulsions, anaphylactic reactions, or meningitis may rarely occur.**(52)** In recent years, measles outbreaks have often been detected and documented, as in the USA or the Netherlands.**(53, 55, 56)** In 2003, a measles vaccination program was launched in Turkey **(52)**, so that all children in elementary school, regardless of vaccination status, were vaccinated to achieve a vaccination rate of 95%. All possible side effects of the vaccinations were immediately transmitted by the family home doctor to the Vaccine Adverse Event Reporting System (VAERS). The vaccination program carried out was able to document the following statistical frequencies of adverse vaccination effects: redness (2097 (1.3%)), swelling of the arm (3597 (2.3%)), arm pain (9836 (6.4%)), abscess (268 (0.1%)), fainting before vaccination (80 (0.05%)), fainting after vaccination (523 (0.3%)), fever (5084 (3.3%)), rash (524 (0.3%)), headache (5433 (3.5%)), vomiting/nausea (2834 (1.8%)), dizziness (24 (0.0015%)), and inflammation of the brain (2 (0.00013%)).**(52)**

The comparison between the descriptive statistics of documented adverse due to the measles vaccination and the frequency of measles symptoms and potentially life-threatening events related to the measles disease effects (e.g. pneumonia, brain inflammation, fever, nausea, vomiting, parotitis, febrile convulsions, anaphylactic reactions, or meningitis) advocates the recommendation of measles vaccination. Moreover, the following description of chosen measles outbreaks and the elevation of

measles cases demonstrates the close connection between the vaccination rate and the frequency of measles diseases.

Between 2007 and 2011, only 118 measles cases were detected and documented in turkey. Due to the past migration circumstances, 8760 new cases of measles were diagnosed in turkey between 2012-2016. The vaccination status of the refugees was mostly not present or not known.**(52)** In 2014, the United States recorded a record number of measles cases, 644 cases from 27 states, more than 3-fold higher than any previous year since 2000. In 2015, the Disease Control and Prevention (CDC) has reported 121 measles cases in 17 states, mostly from an ongoing outbreak linked to a park in Orange County, California.**(57)**

This section of the master's thesis reveals that the practical benefits of the measles vaccination are scientifically proven. This is due to the fact that the measles cases and death rates in Bangladesh **(49, 50)**, Colorado**(51)** , Turkey **(52)**, or the Netherlands **(53)** are associated with the measles vaccination rate. Therefore, the positive effect of the practical benefit of the measles vaccination should be prioritized compared to the side effect rates of the measles vaccination. Since the side effects are mainly unproblematic and non-life-threatening compared to the symptoms of a measles disease it can be argued that the measles vaccination should be recommended for patients, because the benefits surpass the harms. Furthermore, the knowledge benefit of vaccination and the measles virus infection is used to prevent measles virus infections with the live vaccine of the measles virus to establish immunological protection. Moreover, the statistical overview of the side effect rates **(52)** shows that these are lower than the complication possibilities **(36, 47)** from a measles infection. It is important to note that the practical benefits of vaccination and the benefits of knowledge are not accepted and tolerated by all people. Here it becomes clear that the practical and usefulness of knowledge does not necessarily have to be accepted by all people. In the HBA, the concept of benefit must be analyzed precisely to be able to carry out the weighing process with the harm dimension. For this reason, in the next sections, the concept of benefit within the animal research debate will be examined in more detail. In addition to that, based on Regan's animal rights view and Singer's preference utilitarianism, arguments are devised for the respective benefit concepts in the HBA.

For this reason, the term benefit must be further explored in the EU Directive 2010/63/EU passage “(...) ultimately *benefit* human beings, animals, or the environment (...) **(3, 5)**” to get a clearer understanding of the weighting ratio between

expected harms and potential benefits in the HBA. Hence, the master's thesis investigates the conceptualization of benefits in the HBA weighing process by using Brønstad's benefit classification system. According to Brønstad's benefit classification system, benefit concepts are divided up into primary benefits (knowledge benefits (information, skills, understanding, etc.), practical benefits (therapies, conservation, etc.)) and secondary benefits (e.g. career benefits, success, money).⁽⁶⁾ In addition to that, the linguistic expression ethical consideration in the phrase “ (...) the harm to the animals in terms of suffering, pain, and distress, is justified by the expected outcome taking into account *ethical considerations* (...) **(3, 5)**” of the EU Directive 2010/63/EU has to be evaluated in more detail to determine applicable ethical positions in the HBA. Consequently, the research question in this master's thesis is as follows: Can it be justified to prioritize practical benefits over knowledge gains in the harm-benefit analysis within the framework of the animal rights view or preference utilitarianism? Thus, the master's thesis aims to use the animal rights view and preference utilitarianism as ethical justifications for the respective benefit concepts in the HBA to generate suitable arguments whether an animal project or experiment is ethically justified. These arguments support the final decision of the competent authorities whether a certain animal experiment can be performed.

4. Definitions

In the following, the core vocabulary for this master's thesis will be expounded to obtain a basic understanding of the terminology for answering the research question and comprehending the result section. For this reason, the terms "Brønstad benefit classification system", "Harm-benefit analysis", "Tom Regan's animal rights view", and "Peter Singer's preference utilitarianism" are defined. It is important to note that these definitions are not universally used and understood which is why the definition serves as a suitable guide in the animal research debate.

4.1. Brønstad benefit classification system

Brønstad et al. described a benefit classification system in animal research **(6)**. This concept differentiates benefits into primary and secondary benefits. Primary benefits are used as decisive assessment tools in the HBA evaluation process of animal projects, whereas secondary benefits must not be used as justification for the authorization of animal testing procedures. The primary benefits are categorized as knowledge benefits (information, skills, understanding, etc.) and practical benefits (therapies, conservation, etc.). Secondary benefits aim at individual and collective career benefits, success, money, etc.**(6)**

4.2. Harm-benefit analysis

The European Commission, the OIE, and the CIOMS-ICLAS established guidelines to secure minimal standards of animal protection in animal research. EU Directive 2010/63/EU requires that every project involving living non-human vertebrates and cephalopods has to undergo a legally binding project evaluation, including the HBA that comprises ethical considerations (Art. 38 lit d), as part of what is typically called an ethical review.⁽⁵⁾ Therefore, in all European Union member states, legal authorities and ethical committees must follow EU Directive 2010/63/EU and corresponding national law to approve or disapprove projects.⁽⁵⁾ Accordingly, they are confronted with the challenge of quantifying and balancing the 'harms' and 'benefits' of animal use for scientific purposes.^(58–60) Particularly, the project evaluation has to include the following content: "the HBA of the project, to assess whether the harm to the animals in terms of suffering, pain, and distress, is justified by the expected outcome taking into account ethical considerations, and may ultimately benefit human beings, animals, or the environment".^(3, 5) In addition to that, every animal will be classified as worthy of protection (life and embryo vertebrates and cephalopods). Therefore, the terms harm and benefit are defined as accurately as possible within the HBA to weigh both categories in the project assessment process. ^(5, 6)

In this context, I would like to point out the aspect that the concept of "outcomes (= knowledge gain)" is not precisely defined in the HBA definition. Consequently, it is difficult to identify the suitable outcome which may ultimately lead to benefits for human beings, animals, or the environment ⁽⁵⁾. Furthermore, the time frame until a benefit for animals, humans, or the environment can arise is not defined. Moreover, it is crucial to note that the ethical consideration is not discussed or determined how to assess the HBA weighing process. The importance of the HBA analysis for the research question is that a clear understanding of the vocabularies used facilitates the discussion in animal research. In addition to that, the prioritization of the different benefit concepts and the comparison to the harm dimension can be performed easier if the linguistic definition is as exact as possible. The next two sections delineate "Peter Singer's preference utilitarianism" and "Tom Regan's animal rights view". In animal project evaluations, it is crucial for the ethical discussion that all terms are as clear as conceivable to get a common discussion foundation among all different parties. Therefore, "Peter Singer's preference utilitarianism" and "Tom Regan's animal rights

view" must relate to the content of the HBA understanding. Hence, the first step is the comprehension of both ethical positions. In the section "Results" the knowledge of "Peter Singer's preference utilitarianism" and "Tom Regan's animal rights view" will be used to justify the comparison between the expected animal harm and the potential benefits in animal project evaluations.

4.3. Peter Singer's preference utilitarianism

The following section demonstrates Peter Singer's preference utilitarianism to get the key notion of his preference utilitarianism that is necessary to understand the justification reasoning and the arguments for the respective benefit concepts in the HBA. Therefore, the most important aspects of preference utilitarianism will be expounded and discussed below.

Singer argues that the central criterion for integration into the moral community is the sentience of individuals. This sentience is shared by humans and animals. As sentience, Singer describes the ability of individuals as a perception of pain or pleasant feelings (e.g. happiness). The perception of pain or pleasant feelings is sufficient condition for an individual to be given the ability of sentience. The pain dimension is a reasonable premise to speak meaningfully about interests in animals. Therefore, animals can have preferences in terms of fulfilling and not frustrating interests. The sentience is used as a necessary condition to justify the fact that the respective individuals have preferences.**(61)** Preferences serve as a sufficient condition for defining a reasonable limitation of the moral community, regardless of species. Singer claims that one interest counts for one preference. Therefore, from a standpoint of the universe's position, all interests/preferences count equally.**(61)** Hence, Singer argues that the principle of equality represents the standpoint of moral which means the equal consideration and respect of all individual preferences. Singer does not mean that toddlers or animals should be allowed to obtain a driving license or to have the right to vote like adults, just because they are also part of the moral community. The principle of equality means that only comparable preferences should be given equal consideration.**(61)** Singer's preference utilitarianism is a consistent approach, defining good consequences in fulfilling preferences and bad consequences in not fulfilling preferences. The essential distinguishing criterion between preference utilitarianism and hedonistic utilitarianism is that the realization of a preference does not necessarily have to be accompanied by a positive sensation. Singer insists that the criterion of sentience takes on a universalizing character by introducing the impartial observer.**(61)** This gives the respective criterion an objective feature, which is why all individuals would choose the same action and consequences after careful consideration. In addition, the position of the impartial observer is intended to avoid personal prejudices

and preferences. Ethics is not only about asserting one's interests and preferences, but also about taking other perspectives into account.**(61)** Another central element in preference utilitarianism is the principle of aggregation. Here, positive, and negative consequences can be combined and weighed against each other. This means that the preferences of individuals in the moral community are not given absolute protection. This protection is always considered relative to the aggregated consequences. Therefore, the aggregated consequences can be more important than the preferences of an individual. Hence, in preference utilitarianism, it is morally allowed to sacrifice an individual due to a better consequence balance.**(61)** In the decision-making process, it is not important who has the preferences but only how many preferences are affected in the respective situation. Due to the impartial observer, all preferences count equally, regardless of whether the preferences are attributed to humans or animals. Singer describes three criteria to support the preference approach in his animal ethic position. The three criteria are complete information, calm attitude, and clear thinking, so that not all preferences (e.g. taste preferences or drug use) are permissible as a condition for the moral admissibility.**(62)** Singer also differentiates between vital and trivial preferences. Here, the preference of the pig to live is described as a vital preference, whereas the preference to satisfy hunger with pork is declared as a trivial preference. Preferences unite moral- and non-moral beings who belong to the moral community. However, only moral agents can consider preferences from the point of view of the impartial observer. For Singer, preferences must be unbiased and weighed against each other. Singer also differentiates between self-conscious and non-self-conscious individuals. Self-conscious individuals have experiences and possess future preferences, whereas non-self-conscious individuals do not have future preferences.**(61, 62)** According to Singer, non-self-conscious individuals without pain sensation can be killed, because no future preferences can be destroyed.**(63)** Singer is assigned to pathocentrism because all individuals who can suffer are integrated into the moral community.**(64)** However, he is often classified as a sentientist, because the ability of sentience is a natural property, and this is used as a sufficient condition for moral consideration. Singer argues against rationality or language skills as a criterion for integration into the moral community because he is not a representative of speciesism. Here the aspect becomes clear that the scientific findings play an important role, whether they give the respective living beings the ability or not. These

scientific findings are critical to Singer's approach as to whether individuals are integrated into the moral community or not.(63)

In summary, the basic ideas of Peter Singer's "preferences utilitarianism" are described above. The ethical consideration of the reasoning process and the arguments are based on Peter Singer's key concepts such as "sentience", "impartial observer", "principle of equality", "vital and trivial preferences", and the "principle of aggregation". These basic ideas should support the understanding of the reasoning process and arguments for the respective benefit concepts in the HBA. In the following, I am going to explain the "marginal case argument (65)" to show that there is no definitive separation or unique ability between animals and human beings. Therefore, it is important to note that both human beings and animals should be considered equally in the study project evaluation process whether the experiments are allowed to be performed considering harms and benefits in the HBA.

In the literature, the so-called "marginal case argument (65)" is described to show that certain people also do not have a certain ability. In contrast to that, several animals have this certain ability. Therefore, if moral protection is dependent on a certain ability, and we recognize this ability to all human beings, then those animals that possess the ability must also be regarded as morally worthy of protection. The first premise of the argument would be as follows: if a moral status is to be established in full and equal proportions for all and only human beings, then there must be a property P that all and only human beings have such a status. (P1) The second premise explains this aspect: each of the properties P in question is missing from some human beings (marginal cases: wake-comatose, dementia people, embryos, etc.). (P2) The third premise describes the following point: Every property P, which is attributed to all human beings, can also be attributed to (many) animals. (P3) Therefore, the marginal case argument discards that all and only human beings have moral status to the full and equal extent. (C) We take human "marginal cases" into account in our moral community. Hence, we must consider similarly capable animals as morally as well.(65) The validity of the "marginal case argument" remains, as long as we are not able to differentiate between animals and the marginal cases.(66) According to Singer, animal testing is acceptable, if we were to carry out the same experiments on humans.(63)

Synoptically, the "marginal case argument" revealed that no specific ability or feature can clearly distinguish between animal and human beings. Every ability can be found in some animals and every ability can be absent in some human beings. For this

reason, experiments with human beings or animals should be evaluated in ethical commissions because both individuals can suffer from pain or distress. Therefore, the HBA must include the benefit assessment of study projects and the ethical consideration for experiments with human beings and animals as well. Otherwise, there would be an unfair and arbitrary decision-making process in the HBA regarding animal testing procedures or experiments with human beings. If we want a consistent moral position and ethical consideration of moral individuals, then there is the necessity of equal respect of members of the moral community, for example, in testing procedures in study project assessments.

4.4. Tom Regan's animal rights view

The following section is intended to explain Tom Regan's "animal rights view" to gain the necessary understanding of the "animal rights view" that is required to comprehend the justification level and the arguments for the respective benefit concepts in the HBA. For this reason, the essential phenomena of the "animal rights view" are to be delineated and related to each other.

Tom Regan has described a crucial position in the animal rights movement in his work "The Case for Animal Rights"**(67)**. Regan's ethical consideration assumes that individuals in the moral community should be protected from harm and any instrumentalization because of the principle of respect. Moral objects have no duties, but they can act as addressees of moral duties. Furthermore, these individuals should not be sacrificed for the interests of others. Regan operates within the frame of moral individualism.**(67)** On the one hand, the moral quality of an act is determined by compliance with moral duties and on the other hand, there are moral rights that are assigned to individuals without having moral duties. Here, the consequences of action only play a marginal role. Regan states that the inherent value of an individual should be protected in a moral community so that these individuals will not be trumped or sacrificed due to a certain amount of consequences or interests.**(61)** According to Regan, utilitarianism overlooks the fact that in the moral community individuals are beings worthy of protection. Regan also criticizes Peter Singer's preference utilitarianism. Preference utilitarianism is not only about maximizing well-being, but also about the realization of preferences that are differentiated by quantity and not by quality.**(67)** In preference utilitarianism, the distinction between conscious and non-conscious (future preferences) individuals does not convince Regan, because the fundamental problem of offsetting individuals/preference remains.**(67)** For Regan, both humans and animals have moral rights, because all individuals in the moral community have an inherent value. Regan wants to distinguish the inherent value from the intrinsic and instrumental value. The instrumental value is that an actor wants to achieve a specific goal. For example, the instrumental value of a key is that it can open a certain door. The intrinsic value expresses positive or negative experiences of sensitive beings. The joy or satisfaction of preferences can have an intrinsic value. The

instrumental and intrinsic values are both actor-relative and situation-dependent. By contrast, the inherent value is independent of actors and the interests of others, which is why it cannot suffer a loss of value. In addition to that, the inherent value must be considered inconsequentially and logically independent of the instrumental and intrinsic value. The inherent value is shared by all individuals in the moral community. This gives all individuals the privilege of moral rights for their own sake.**(62, 67)** For Regan, both moral agents and moral objects have an inherent value that cannot act morally themselves. According to Regan, animals are to be classified as moral objects that are recipients of moral acts because of the moral principle. Moral objects have no duties, but they can act as addressees of moral duties. Here, Regan argues that the similarity between direct and indirect obligations cannot be confirmed, because indirect consideration of moral objects is not a plausible approach. We have direct duties towards a being itself, whereas indirect duties mean that moral objects are worth protecting because I am supposed to treat an actor's property morally.**(67)** For this reason, Regan supports his position with the non-harm principle, because moral objects (animals) have an "experiential welfare" that should be protected from physical or psychological suffering. The non-harm principle is treated by Regan as a prima facie principle. Regan argues that this prima-facie principle is confirmed by our moral intuition, which is why this principle also directly benefits moral objects. Hence, he describes those individuals (moral agents and moral objects) should not be harmed in the moral community. Therefore, actions that harm individuals in our moral community are morally wrong because they limit their well-being. Regan's approach and the principle of non-harm are reinforced by four further criteria. The criteria are called consistency, reasonable distance, precision, and conformity with thoughtful intuitions.**(67)**

The criterion of consistency is that the principle of non-harm should always be applied to comparable harms of moral actors and moral objects, otherwise an inconsistent moral position would arise. The reasonable distance is that, on the one hand, many cases must be covered, and on the other hand, there is a reasonable limit that is achieved by the inherent value and the property of subject of a life. As precision, Regan argues that ethics are aimed at avoiding harm that he tries to achieve through the principle of non-harm.**(67)** The criterion of conformity with thoughtful intuitions refers to the fact that a better principle must be reasonably established that covers more essential moral intuitions if the principle of non-harm should be substituted. An

individual (human or animal) has an inherent value if it has the property "subject-of-a-life". The property "subject-of-a-life" can express itself, for example, perception, memory, preferences, idea of one's future, or desires in an individual. The "subject of a life" property illustrates the similarity between moral agents and moral objects because the decisive characteristics are shared.**(67)** The fact that individuals with the criterion "subject of a life" have an inherent value is justified by Regan's intuition that a criterion for attributing an inherent value must set a limit for the moral community.**(67)** In addition, the criterion should be able to perform the either-or functions, whether the individual has the relevant properties or not. Furthermore, the criterion must occur in the case of moral agents and moral objects. The three aspects of an appropriate criterion mentioned above are reasonably considered and fulfilled by the criterion "subject of a life". In conclusion, Regan describes the principle of respect that ascribes to every individual in the moral community. This principle of respect states that everyone must be treated equally in terms of moral rights and respect. The principle of respect is fulfilled when the inherent value of an individual is considered, and no individual is harmed to gain benefits for others. Due to the inherent value, the principle of respect makes it clear that the aggregation principle of utilitarianism is untenable. The inherent value cannot be sacrificed for moral reasons through optimal consequences and a better benefit balance. Regan's position is called abolitionism.**(67)** Any unjustified animal testing or other animal experiments in various fields (e.g. agriculture or food production) will be prohibited. Reagan's approach is egalitarian and non-perfectionist that ascribes an inherent value to every moral individual. In addition, the inherent value expresses that everyone has an intrinsically value. For Regan, toxicological studies are unjustifiable because scientific validity is being questioned and we now know so much that we have alternatives to animal testing concerning toxicity. Another option would be to ban those products that need animal testing. Regan refuses to take stock of animal harm and benefits. However, he stresses that knowledge is still important, but only if the above principles (inherent value, etc.) are not violated. Subjects should be able to agree to preserve the principle of respect.**(103, 105)**

To sum up, it can be stated that the understanding of Tom Regan's "animal rights view" should help to better understand the arguments for the respective benefit concepts in the HBA. The ethical consideration of the arguments is based on Tom Regan's

essential concepts such as "principle of respect", "non-harm principle", "subject of a life", or "experiential welfare".

5. Aim of the master's thesis

This master's thesis aims to evaluate, investigate, and critically examine the benefit concepts in the HBA. In addition to that, the secondary purpose of the master's thesis is the investigation of the conceptualization of the benefits by using Peter Singer's preference utilitarianism **(61)** and Tom Regan's animal rights approach **(67)**. The increasing interest of the population in scientific research with animals has the consequence that researchers, politics, media, and journals must deal with this topic in more detail. The competent authorities in the European Member States must perform the HBA before animal projects are allowed to be conducted. This HBA guideline is defined in the EU Directive 2010/63/EU**(5)**. The competent authorities have to judge the expected harms (e.g. suffering, pain, and distress) on animals within an experiment and weighed the potential benefits (for humans, animals, or the environment) against the expected harms on animals to determine the final approval decision of a certain animal testing experiment.

The phrase “(...) ultimately *benefit* human beings, animals, or the environment (...) **(3, 5)**” of the EU Directive 2010/63/EU should be analyzed in more detail because the term benefit is not clearly defined yet. The term benefit is crucial for the HBA process to weigh these potential benefits against the expected harms on animals. Hence, this master's thesis investigates the conceptualization of benefits in the HBA weighing process by using Brønstad's benefit classification system. According to Brønstad's benefit classification system, benefit concepts are divided up into primary benefits (knowledge and practical benefits) and secondary benefits (e.g. career benefits, success, money).**(6)** In addition to that, primary benefits are classified into knowledge benefits (information, skills, understanding, etc.) and practical benefits (therapies, conservation, etc.). Primary benefits are used as decisive assessment tools in the HBA evaluation process of animal projects, whereas secondary benefits must not be used as justification for the authorization of animal testing procedures.**(6)**

6. Methodology

To identify benefits or benefit concepts and suitable arguments as well as reasons within the framework of the animal rights view or preference utilitarianism regarding the HBA, a systemic review of reasons was performed. A systemic review of reasons can be used to identify reasons and arguments for the benefit concepts, preference utilitarianism, or animal rights view in the HBA. For this purpose, a systematic review of reasons, as suggested by Strech and Soafer **(68)** was carried out to specify lines of argumentation within a particular debate such as the animal research debate.

Therefore, this methodological approach can specify how the benefit concepts are justified and the preference utilitarianism or animal rights view generate suitable arguments in the current debate of HBA. A literature search of the PubMed database was performed to identify all relevant articles for this question. PubMed was chosen because new research articles and historically important articles in biomedical animal research are accessible there **(for detail see Figure 1)**. PubMed has broad coverage, with a focus on the natural sciences and interdisciplinary research. The search strategy included variations on pairs of terms: animal research, benefit, harm-benefit analysis, benefit concept, animal experiment, moral ethical justification, and animal experimentation **(see Table 1)**.

Brønstad et al. described a benefit classification system in animal research **(6)**. This concept differentiates benefits into primary and secondary benefits. Brønstad's benefit classification system shows that primary benefits are graded into knowledge benefits (information, skills, understanding, etc.) and practical benefits (therapies, conservation, etc.). Primary benefits are used as decisive assessment tools in the HBA evaluation process of animal projects, whereas secondary benefits must not be used as justification for the authorization of animal testing experiments. Therefore, only potential primary benefits (for humans, animals, or the environment) are used in the HBA to weigh these benefits against the expected harms on the animals.**(6)** The search process took place between October 2019 to May 2020.

First, a relevant text passage was identified in each article due to the inclusion criteria. Next, narrow, and broad types of reasons were generated. If different articles mentioned the same narrow or broad type of reasons, I subsumed every suitable article into the narrow or broad type of reasons.

Second, I used the benefit classification introduced by Brønstad et al. 2016 **(6)** to categorize the benefits and benefit concepts found in the literature. Brønstad and colleagues suggest differentiating between practical benefits like medical therapy, species conservation, etc., knowledge benefits such as skills, understanding information, etc., and so-called secondary benefits, under which positive impact on reputation or career are subsumed.

The aim at this point is not a normative or critical evaluation of these different kinds of benefit, but a mere description of how the benefit is dominantly conceptualized in the current animal debate. The predetermined concept of Brønstad et al. implies that the benefits of each study must be classified into a certain benefit concept **(6)**. During the literature search and the processing of the papers, different study benefits and justifications for animal trials were determined using narrow and broad types of reasons.**(68)** The explanation of the broad types displays that, at first, general terms were defined (e.g. ethical animal position) and, in the course of the literature search, more precise descriptions could be made so that narrow types could be identified (e.g. preferentialism, animal rights view). For this reason, I looked for what the respective authors of the papers described as reasoning and/or benefits to expound a vindication for performing animal experiments.**(6) (68)**

To find many articles in the PubMed database concerning benefit concepts, animal rights view, or preference utilitarianism to answer the research questions, I put the sensitivity of the article selection process as high as possible. Mainly, the article selection process contained two steps:

1. Searching for the inclusion criteria in all abstracts, titles, and keywords of each article (see below)
2. Searching for the broad and narrow types of reasoning in the selected articles due to the inclusion criteria

The following inclusion criteria have been determined:

1. The article included an animal ethics position in the animal research debate.

It is important to note that the first criterion represents an ethical position in the animal research debate and that the article is directed towards a particular aim. For instance, the argumentation and vindication in utilitarian preferentialism aim to reduce pain and maximize the good in society or animal lives.

For instance, in Tannenbaum's paper, he demonstrated the "knowledge justification" by analyzing five elements of the knowledge concept. Tannenbaum delineated five elements: factual knowledge, experiential knowledge, contemplation, intellectual activities, and pleasures/frustrations.**(29)** Tannenbaum defines intellectual activities as intellectual faculties or skills that can also be generated from the knowledge and may be important for researchers to carry out animal researches. His decisive point reveals that the curiosity-driven interest of the researchers to investigate certain questions is equally important compared to pleasures or pain within the utilitarian perspective.**(29)**

2. The article included a description of the benefit concept in the harm-benefit analysis. The second criterion indicates that there are different benefit concept descriptions in the literature articles concerning the formulations and variations on pairs of terms used for the article searching process.

For instance, Brønstad et al. delineated a benefit classification system in animal research **(6)**. According to his classification system, he distinguishes between primary and secondary benefits. Primary benefits are divided up into knowledge benefits (information, skills, understanding, etc.) and practical benefits (therapies, conservation, etc.). In contrast to that, secondary benefits aim at individual and collective career benefits, success, or money advantages. Moreover, primary benefits are used as decisive assessment tools in the HBA evaluation of animal projects, whereas secondary benefits must not be used as vindication for the authorization of animal experiments. **(6)**

3. The article included a description of a minimum of one modulating factor for any benefit in harm-benefit analysis.

The third criterion displays the modulating factors, indicating the level of reflection within the project evaluation process regarding transparency, scientific validity, research design, or statistics. Modulating factors in the HBA indicate those factors which influence the weight of the respective benefit concept. For instance, a bad scientific validity leads to a weak knowledge foundation and following a probably useless scientific gain in a certain research area.

For instance, Würbel underlines the 3Vs to optimize scientific validity. The evaluation of the constructed validity (cV) is based on the evidence about the level of agreement between the animal model, the outcome variable, and the quality to be measured. The evaluation of the internal validity (iV) is based on the evidence for scientific rationality (e.g. suitable control groups) and the scientific rigor (e.g. reduction of risk bias, sample sizes calculation, randomization, blinding, statistical planning, and definition of primary/secondary outcome variables). The evaluation of the external validity (eV) is based on the evidence for experimental design features that facilitate inference to other populations so that the reproducibility and generalizability are comprehensible and consistent. Therefore, the 3V concept depicts an important instrument for optimizing and assessing scientific validity and therefore, increasing the probability of achieving the potential benefits of animal projects.(69)

During the literature research, it turned out that only English-language texts could be found since no suitable German-language texts could be identified in the above-mentioned database. Therefore, no German articles were used in the analysis. Hence, this methodological approach introduces a "selection bias" and a "language bias" because only English articles have been included in the analysis section. Articles were used if at least one inclusion criterion from criteria 1-3 was fulfilled.

All abstracts, titles, and keywords were screened. The search terms checked whether the abstract or the title of an article included these terms or not. If an article (abstracts, titles, and keywords) matched the inclusion criteria, then the entire text was worked through. The reference lists of included articles were checked for further relevant articles (=snowballing). I expected a significant increase in the relevant literature through "snowballing" due to the concentration of the literature search on titles, keywords, and abstracts. About 25 percent (23,68%; 19 out of 76) of the included articles were determined by the snowballing process. I concluded that this can be ascribed to two factors. Firstly, older texts (in the 1980s or 1990s) are not accessible

in the databases. Secondly, the terminology regarding modulating factors is not handled uniformly in the literature and this factor depicts the largest proportion of all articles found by the snowballing process.

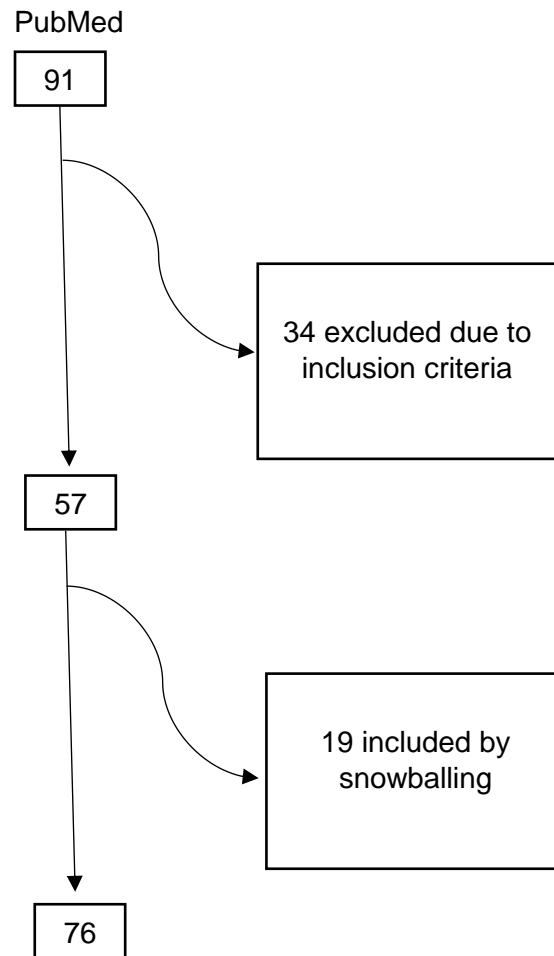


Figure 1. Flow chart of article selection and inclusion. **Adapted from (70)**

In **Table 1**, all variations on pairs of terms are delineated and the search strings used in the PubMed database are listed.

| Focus | Search string |
|---|--|
| animal experimentation and/or animal research and/or benefit and/or harm-benefit analysis | ("animal experimentation"[MeSH Terms] OR ("animal"[All Fields] AND "experimentation"[All Fields]) OR "animal experimentation"[All Fields] OR ("animal"[All Fields] AND "research"[All Fields]) OR "animal research"[All Fields]) AND benefit[All Fields] AND harm-benefit-analysis[All Fields] |
| animal experiment and/or animal research and/or benefit concept | ("animal experimentation"[MeSH Terms] OR ("animal"[All Fields] AND "experimentation"[All Fields]) OR "animal experimentation"[All Fields] OR ("animal"[All Fields] AND "research"[All Fields]) OR "animal research"[All Fields]) AND benefit[All Fields] AND concept[All Fields] |
| benefit and/or animal experiment and/or animal experimentation | benefit[All Fields] AND ("animal experimentation"[MeSH Terms] OR ("animal"[All Fields] AND "experimentation"[All Fields]) OR "animal experimentation"[All Fields] OR ("animal"[All Fields] AND "experiment"[All Fields]) OR "animal experiment"[All Fields]) |
| moral ethical justification and/or animal experimentation | ("morals"[MeSH Terms] OR "morals"[All Fields] OR "ethical"[All Fields]) AND justification[All Fields] AND ("animal experimentation"[MeSH Terms] OR ("animal"[All Fields] AND "experimentation"[All Fields]) OR "animal experimentation"[All Fields] OR ("animal"[All Fields] AND "research"[All Fields]) OR "animal research"[All Fields]) |

Table 1. Key search strings (Adapted from (68))

The methodological section expounds on the chosen approach to determine the content and to answer the research question. For this reason, the inclusion criteria were delineated, the review of systemic reasons with the broad and narrow types was explained, the search strings were listed, and the article selection process was elucidated (68). In the following, I am going to demonstrate the results of the master's thesis, which could be explored through the retrospective systematic literature review of reasons.

7. Results

This chapter of the master's thesis is intended to show the results of the retrospective systematic literature review.

The primary aim of this master's thesis is to identify suitable and reasonable benefit concepts that can be used in the HBA weighing process. Firstly, the findings of the different benefits listed in the articles concerning animal experiments are presented. In addition to that, the respective benefits are assigned to the benefit concepts according to the Brønstad classification system **(6)**. Subsequently, a quantitative list of the articles in the PubMed database is shown based on the primary and secondary benefit concepts.

The secondary aim of the master's thesis is that the conceptualization of the benefit is investigated by Peter Singer's preference utilitarianism **(61)** and Tom Regan's animal rights view **(67)**. The animal rights view and preference utilitarianism can expound arguments and reasonings which are used to determine arguments for or against the final decision of projects with animal experiments. For this reason, ethical considerations such as the preference utilitarianism and the animal rights view are used to explore arguments and justifications for or against the conduction of animal experiments. The arguments and justifications of these ethical positions (the preference utilitarianism and animal rights view) are carried out for both the primary benefit concepts (knowledge and practical benefit concepts) and the secondary benefit concept. These arguments may support the final decision of the competent authorities whether a certain animal experiment can be performed.

7.1. Concrete benefits from animal testing

In the following, I am going to list each benefit found in the articles and assign them to the benefit concepts according to the Brønstad benefit classification system. This benefit classification concept distinguishes benefits into primary and secondary benefits. Primary benefits are classified into knowledge benefits (information, skills, understanding, etc.) and practical benefits (therapies, conservation, etc.). In addition, secondary benefits aim at individual or collective career benefits, success, money, etc. **(6)** The reason for choosing the Brønstad benefit classification system was due to the suitable benefit concepts (primary and secondary benefits) which guaranteed that every benefit could be assigned to one of these benefit concepts. In addition to that, the benefit concepts (primary and secondary benefits) facilitated a comprehensible comparison between the findings in the articles found on the PubMed database.

In the current literature, many benefits can be found in different research fields. On the one hand, the concrete benefits can benefit each individual or the entire population. **(71)** In medicine, the benefits could be used as a practical benefit for medical practitioners, patients, or animals. There are many practical benefits described in the literature, such as health **(72)**, medical therapies **(73)**, optimized quality of life **(74)**, a medical-technical advance **(21, 75, 76)**, further improvements in treatment, rehabilitation progress **(1, 9, 77, 78)**, the use of antidotes **(79)**, or vaccinations. **(80)** In addition, further benefits are characterized in the toxicological field **(81)**, in sanitary facilities, in the ecological and economic domain, and the educational system **(82–86)**. The benefits can also be used for the conservation of animals. **(87)** In addition, benefits from animal experiments in the forensic field were also taken into account, so that, certain identification tests could be detected. **(6, 88, 89)** The listed benefits are discussed in the applied research area and are feasible with a certain probability. The concept of probability implies that the project evaluation must also differentiate between current/actual and potential benefits since both scientific and non-scientific factors contribute to whether a potential practical benefit will be socially integrated or not. **(6)** In contrast, basic research generates fundamental knowledge that will be used in applied research projects. For this reason, many authors consider knowledge itself to be an essential benefit. Moreover, the progression of knowledge is also a desirable goal itself. **(69, 80, 90–94)** In addition, the knowledge can be further used for skills and educational purposes. **(29)** Furthermore, other personal benefits, such as career,

personal or collective success, or reputation could be found in the literature. These can bring social, family, monetary, individual, or institutional benefits to society.(6)

Table 2 displays all concrete benefits mentioned in the current literature regarding animal testing projects. These benefits in each article were assigned to the benefit concepts according to the Brønstad benefit classification system **(6)**. Each number in table 2 represents one article with the respective benefit under the specific benefit concept such as medical therapy (= concrete benefit) under the benefit concept practical benefits.

How advantages are considered as benefits in the current literature (according to the Bronstad classification) concerning study aim evaluation.

| Advantages found in literature articles | | | | | |
|---|--|--------------------------------|------------------------------------|--------------------------------------|---------|
| <u>Practical benefits</u> | | | | | |
| practical benefit (80, 92, 95–105) | medical therapies (6, 9, 71, 74, 76, 78, 85, 88, 92, 95, 106, 107) | optimized quality of life (74) | medical-technical advance (76, 84) | treatment improvements (21, 106–108) | |
| rehabilitation progress (77) | antidotes (108) | vaccinations (88) | species conservation (85, 88, 109) | forensic (6, 88) | benefit |
| health (2, 6, 72, 74, 82, 83) | ecological benefits (82, 83, 85, 88, 109) | | | | |
| toxicological testing (3, 81) | safety (6, 84, 85) | | | | |
| <u>Knowledge benefits</u> | | | | | |

| | | | | |
|---|--|------------|---------------------|------------------|
| knowledge benefits (9, 21, 29, 71, 76, 80, 83, 88, 90, 93–95, 109– 112) | knowledge progression (6, 29, 90, 91) | facts (29) | information (29) | skills (29, 109) |
|---|--|------------|---------------------|------------------|

**Secondary
benefits**

| | | | | |
|-----------------------------|--|--|----------------------------------|-------------------------------|
| career (6) | personal or collective success (6) | reputation (6) | monetary benefits (6, 113) | institutional benefits (6) |
| personal benefits (6) | educational benefits (6, 85, 88) | economic benefits (2, 6, 82, 85) | | |

Table 2. All advantages are cited that can be translated into benefits.

7.2. Findings in a quantitative perspective

In **Figure 2**, the results of the systemic literature review depict an overview along with the disciplinary differentiation (PubMed) of the selected database (**see Figure 2**). In Figure 2, the results of the systematic review are visualized to provide an overview of all mentioned articles concerning knowledge, practical, and secondary benefit concepts. Figure 2 displays the article number of the PubMed database following the Brønstad benefit classification system in terms of primary and secondary benefits (Figure 2A). Furthermore, we divided the primary benefit into knowledge and practical benefit categories (Figure 2B).

The focus on primary and secondary benefits in the PubMed database showed that the majority of the current articles in the animal research debate lie on the primary benefits (primary benefits $n= 28$ vs. secondary benefits $n=6$; Figure 2A). Dividing primary benefits into knowledge and practical benefits, I found that practical benefits outweighed knowledge benefits (23 vs. 16; Figure 2B). Many articles include both knowledge and practical benefits as well as secondary benefits. For this reason, the sum of knowledge and practical benefits is not equal to the primary benefits.

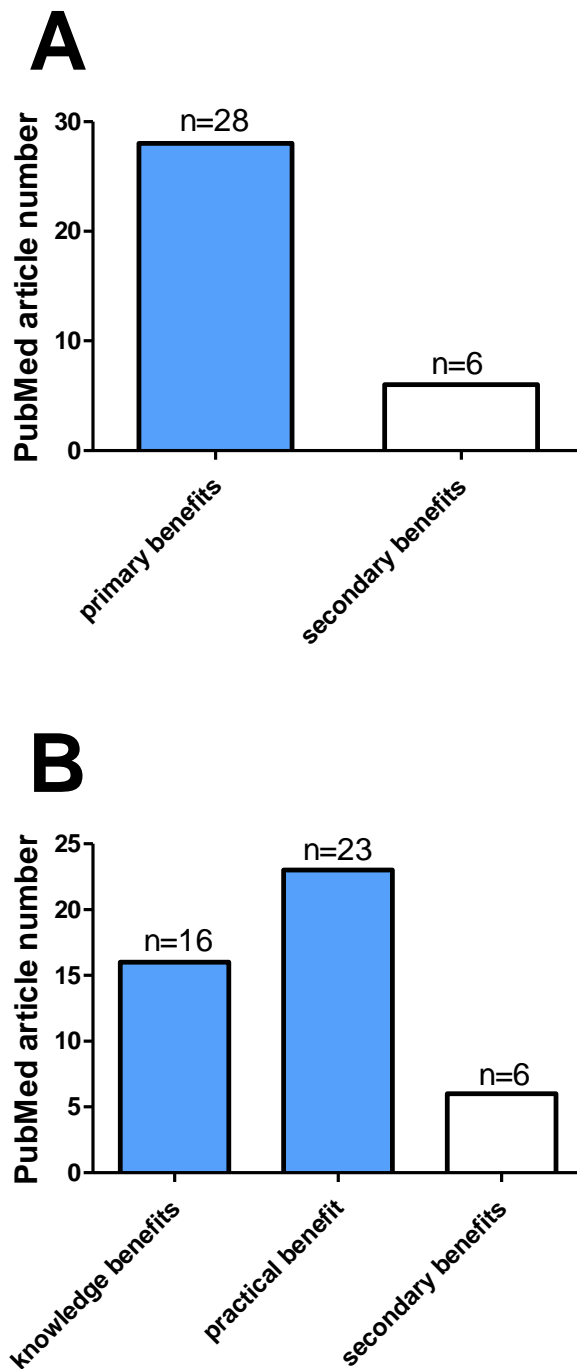


Figure 2. The differentiation in articles of the PubMed database is displayed following the Brønstad benefit classification system (Figure 2A). Furthermore, we divided the primary benefit into knowledge and practical benefit categories (Figure 2B).

7.3. Practical benefits versus knowledge benefits

The measles vaccination situation represents the aspect that knowledge of vaccination and its proven effects as well as the practical application of vaccination in society, do not have to go hand in hand. For this reason, it is essential to consider and analyze the knowledge benefit and the practical benefit separately. The situation of the ethical project assessment of animal experiments in the European Union is remarkably similar. Applicants must comply with EU-Directive 2010/63/EU **(5)** to be allowed to perform animal experiments. The EU-Directive 2010/63/EU requires that the ethical commissions carry out the HBA that considers and assesses the balance of animal suffering with the potential benefits. On the one hand, the HBA determines the pain dimension of the animal as precisely as possible. On the other hand, the potential benefits, such as knowledge or practical benefits, are assessed and evaluated for their importance and necessity.**(5)**

The question arises as to whether the practical benefits or the knowledge benefits should be given a higher weight so that an animal experiment is considered ethically justifiable according to the preference utilitarianism or the animal rights view. The vaccination example highlights the fact that many animals were used to produce the knowledge we are using today to prevent serious infectious diseases **(30, 31)**. Anti-vaccination activists and critics of vaccination can speak badly of the practical benefits of the findings, which makes the practical benefit more crucial than pure knowledge. This would mean that within the weighting process of the HBA, the practical benefits should be considered more important than knowledge itself. But it is a necessary condition to have scientifically proven knowledge to be able to derive potential practical benefits. This shows the point that practical benefits require solid knowledge, but knowledge does not have to imply a practical benefit. Furthermore, this differentiation shows an additional distinguishing feature between the benefit concepts (knowledge and practical benefits). However, it must be stressed that the responsibility of researchers seems to be overwhelmed when they must prospectively define the practical benefits **(9, 71)**. The extra-scientific factors can influence the use of practical benefits in society through the market, profitable production, and efficient distribution circumstances **(69)**.

For this reason, the upcoming chapters highlight, assess, and discuss the benefit concepts (knowledge and practical benefits) and describe their influence on the HBA within the framework of the preference utilitarianism and the animal rights view.

7.4. Operational aspects of benefit concepts for the justification of animal experiments

This section shows that the benefit concepts (knowledge benefits, practical benefits, or secondary benefits) can be morally supported or attenuated by aspects in the HBA. In the literature, several factors have been mentioned which can play a decisive role in the benefit concept evaluation process. In addition to that, all aspects will be used in the upcoming section regarding Peter Singer's preference utilitarianism **(61)** and Tom Regan's animal rights view **(67)** to explore arguments for or against the final decision of projects with animal experiments. The aspects should serve as a justification foundation in terms of prioritizing knowledge, practical, or secondary benefits. Every aspect will be analyzed from the perspective of Peter Singer's preference utilitarianism **(61)** and Tom Regan's animal rights view **(67)** both primary benefit concepts (knowledge and practical benefit concepts) and the secondary benefit concept.

The first aspect is that the assessment of the knowledge benefit, the practical benefit, and the secondary benefits are always influenced by the future aspect. Before animal testing, it is not possible to predict a definitive benefit with 100% certainty. For this reason, the potential knowledge from animal experiments should always be assessed, considering certain areas of research. It is also of great importance that the future aspect of the potential practical benefit will profit societies and individuals so that these practical benefits are accepted and used by many persons in society. For this reason, the future aspect can both strengthen and undermine the weight of knowledge benefits and practical benefits in the HBA, as future circumstances do not have to be promising.**(114) (9)**

The second aspect includes the probability and prediction character of animal research results. There is a reasonable justification for promoting those animal projects that are more likely to generate a knowledge benefit or practical benefits. As a result, less likely research designs would waste relevant human resources, such as personal, temporal, or financial resources. For this reason, the probability aspect can both support and weaken the weight of knowledge benefits and practical benefits in the HBA, because the probability can significantly influence the occurrence of a knowledge benefit or practical benefit from animal testing procedures.**(9, 71, 88)**

The third aspect describes local or global matters, which is why animal testing is carried out. It is a legitimate question whether locality should play a decisive role in the ethical assessment of animal projects. Should animal testing procedures be ethically allowed if the knowledge benefits or practical benefits will profit those people who are located near Europe? For this reason, the localization aspect could both support and undermine the weight of knowledge benefits and practical benefits in the HBA.(29, 115)

It is also important that the aspects are evaluated and discussed from a certain ethical position. Therefore, the three aspects (future aspect, probability aspect, and localization aspect) are assessed with both Singer's preference utilitarianism and Regan's animal rights view to determining reasonings for or against the final approval of animal projects. The relevance to the research question is that the permission to carry out animal projects can be supported or refuted by ethical positions. Here, the animal harm is weighed against the potential benefits and reflected on whether the overall benefit is ethically justifiable or not. For this reason, the ethical justification of animal projects must refer to certain factors such as the future aspect, probability aspect, and localization aspect.

7.4.1. Modulating factors of benefit concepts

In the following, I am going to elucidate crucial factors that influence the weight of the respective benefit concept. For this reason, I am going to call those factors “modulating factors”, because they can modulate the weight of the benefit concept like the scientific validity modulates the weight of the knowledge benefit.

The more likely and the earlier something is considered beneficial, the better for the justificatory power on the benefit side in the HBA. The same logic underlies the part of the debate dedicated to the modulating factors, such as transparency, scientific validity, research design, and statistics **(69, 81, 85, 91, 116–118)**. These factors may be substantial in the discussion because they influence the weight of the benefit. Porter evaluates projects according to each project’s “realistic potential of an experiment to achieve an objective **(1)**”, and projects that are likely to be successful score higher than projects whose outcome is uncertain **(1)**. The likelihood of the benefit (scientific and/or practical) is an important criterion for the study project assessment according to Bout et al.**(83)**.

The following chapter discusses the modulating factors that are considered decisive in the literature as to whether the benefit concepts of knowledge, practical benefits, or secondary benefits are reasonably achievable. All modulating factors can contribute to whether the weight and assessment of knowledge or practical benefits are encouraged in the HBA.

The AALAS-FELASA Working Group concluded that the implementation of the HBA is a systematic approach, but it does not necessarily take the description and definition of benefits, although a good experimental design is a fundamental criterion, so that benefits can be generated from the project at all. For this reason, Würbel introduced the 3Vs to maximize scientific validity. The assessment of the constructed validity (cV) is based on the evidence about the level of agreement between the animal model, the outcome variable, and the quality to be measured. The assessment of the internal validity (iV) is based on the evidence for scientific rationality (e.g. suitable control groups) and the scientific rigor (e.g. reduction of risk bias, sample sizes calculation, randomization, blinding, statistical planning, and definition of primary/secondary outcome variables). The assessment of the external validity (eV) is based on the evidence for experimental design features that facilitate inference to other populations so that the reproducibility and generalizability are comprehensible and

consistent. Therefore, the 3V concept (cV, iV, and eV) is a meaningful tool for optimizing and evaluating scientific validity and thus, increasing the probability of achieving the expected benefits of animal experiments.**(69)** The above-mentioned aspects are essential for reliable knowledge benefit from the animal experiment. It also increases the likelihood of using a practical benefit because it is derived from knowledge. The application of the practical benefit must be classified as more uncertain if the knowledge has been built up on a brittle scientific foundation.**(69)**

Other important aspects are transparency and reporting within the scientific community. Both the negative and the positive results of research projects should be presented to the scientific community. Consequently, research resources are not wasted unnecessarily (time, personnel, financial, etc. resources) by spreading all study information. In advance, this prevents that many study designs will be performed a second time and many animals need not be sacrificed unnecessarily because the required study data have been published. For this reason, several reporting guidelines (ARRIVE **(80)** or GSPC**(119, 120)**) have been established to implement a better reporting habit of researchers, reviewers, and journals. Moreover, the reliability of animal models **(75, 116)** and the choice for a suitable animal model for one's projects could be easier selected if the necessary data were available publicly. Not every animal model is acceptable to all research requirements, which is why it seems essential to disseminate knowledge in this respect. Furthermore, the epistemological recognitions are further optimized when better animal models are selected for research purposes.**(9, 76, 78, 80, 85, 85, 88, 90, 119–123)** In addition to transparency and reporting, the selection and conception of a suitable study design and statistical implementation are essential for gaining knowledge. Therefore, the data on statistical implementation, randomization, sample-sizing, etc. are also crucial for the scientific community.**(69, 81, 91, 124, 125)** For this reason, systemic reviews would be an appropriate tool for retrospectively verifying the reliability of the study designs and evaluating the choice of animal models whether the animal experiments in a particular research field are reliable and valid at all. Thus, scientific validity would be constantly re-controlled and increasingly improved.**(71, 72)**

In literature, the "reproducibility crisis" has developed, which is to be broken down below. The reproducibility cannot be achieved if the scientific standards in an animal research project are not fulfilled, due to a lack of reporting and transparency. Therefore, the repetition of study data cannot be reached by other researchers. The

"reproducibility crisis" in preclinical biomedical research is making headlines at a staggering rate. Spectacular examples of translational failures and poor reproducibility **(126, 127)** have been attributed to various aspects of poor experimental design and conduct, including small sample sizes **(128)**, risks of bias **(129, 130)**, selective reporting **(131)**, and publication bias **(132)**. By interplay the researchers, reviewers, journals, the implementation of the existing guidelines (ARRIVE **(80)** or GSPC **(119, 120)**), and a heeding of the errors described above, many unnecessary resource wasting could have been prevented.**(133)**

Reichlin and colleagues **(133)** conducted an online survey in which 1891 individuals were contacted, of which 530 partially and 302 filled out the questionnaire, with which further analyses were performed. Respondents come from a variety of research fields, such as Molecular Biologic, Veterinary Medicine, or Zoology. The authors examined the difference between self-assessment and systemic reviews in the literature regarding the publication of different risk biases. Therefore, the authors tried to find out whether the participants surveyed were aware of the different risk biases in a study design and whether there is also a serious integration in their studies. Reichlin and colleagues analyzed that the ARRIVE guidelines were known at about 43.7%. They were also able to find out that, for example, the "selection bias" was 65.2% known and 17.9% considered irrelevant. The selective reporting was known in 57.5% and 17.5% considered this to be irrelevant. As possible reasons, the participants mentioned that it was not necessary, that there were space restrictions of the journal, or that they did not think about it. For this, the authors stressed that both the reviewers and the journal itself had to create framework conditions to ensure scientific stringency. They also mention the importance of better training of scientific integrity, training of scientific practice, prevention of ignorance of scientific standards, and creation of incentives. Poor scientific validity implies important scientific, economic, and ethical consequences (e.g. higher drug costs, care costs, or false hopes in the population).**(133)**

In addition to the aspects discussed so far, the responsibility of researchers, reviewers, and journals is also indispensable to maximize the benefit concepts. The integration of scientific standards and reduction of bias/errors should be carefully considered by the researchers, reviewed by the reviewers, and required by journals as a necessary condition. In addition to the methodological and statistical criteria, as well as transparency, reporting, and disclosing the study results for the scientific

community, researchers, reviewers, and journals should be responsible for circumventing the animal testing procedures.(85, 90, 91, 124, 134) Franco and colleagues (134) conducted a survey in Portugal in which they acquired 206 participants from 8 different research laboratories. This questionnaire included the aspects of whether and to what extent the 3R principles are observed and are aware of the respective researchers. One year later, 91 participants were asked again in a follow-up whether they had gained a better understanding and awareness of the 3R principles in their studies through the training courses.(134) The authors argue in favor of the "4R principles" since the responsibility of the researchers plays a decisive role in the extent to which the 3R principles are considered in the research protocols. The experience had been significantly different in the 8 laboratories. 68% of the subjects were women, with the age of the population being between 22 and 60 years. 46% of the subjects claimed that no scientific progress could be made without animal experiments, while 12% stated the opposite.(134)

In summary, the debate on reasonable prospective benefits in animal research, more detailed ideas, and aspects have been formulated and described over time. An essential point is the collective dissemination of the explored research information and the publication of the generated results so that the same studies do not have to be carried out many times and therefore further animals have to be harmed ("Good scientific practice").(4, 5, 7, 21–23, 26) In addition to that, the ethical committees discuss whether the research protocol shows certain originality and feasibility to waste no time, financial, and human resources.(1, 2, 22). In ethical project evaluations, several modulating factors are important for a positive ethics decision. An important point is the quality of the experimental design, in terms of whether the different bias in the study design is considered and minimized. Moreover, the probability of research success plays a crucial role, which can be maximized by a retrospective assessment of existing knowledge.(6)

This section revealed the main modulating factors that can modulate the weight of the benefit concepts and thus influence the weighting ratio between expected harms and potential benefits in the HBA. In addition to that, the aspect of modulating factors showed that the justificatory power of benefit concepts is dependent not only on the study project design but also on modulating factors such as transparency, scientific validity, research design, and statistics (69, 81, 85, 91, 116–118).

7.5. The weighting of knowledge, practical, and secondary benefits in terms of justification in animal research

The following chapter presents the benefit concepts (knowledge, practical, and secondary benefits) in the face of Singer's preference utilitarianism and Regan's animal rights view. Moreover, relevant aspects (future, probability, and local aspects) that can be used for knowledge benefits, practical benefits, or secondary benefits are used. The analysis of the knowledge benefits, practical benefits, or secondary benefits within the framework of the preference utilitarianism or animal rights view helps us to find suitable arguments for the final approval of study projects with animal experiments. Furthermore, this section tries to determine reasons and arguments whether knowledge, practical, or secondary benefits show the most important impact on the ethical consideration concerning study projects with animal experiments.

7.5.1. Justification by Preference Utilitarianism

7.5.1.1. Knowledge benefit

The first aspect represents the future aspect of knowledge. The generated knowledge from the animal experiments can be integrated into an existing theory building as well as the exclusion of knowledge has relevance for a particular research area. For this reason, any knowledge for sentient beings (humans and animals) can be reused, which is why the future aspect leads to an advocacy of the knowledge benefit. Consequently, the generated knowledge can benefit future human beings because of its value in a certain research area like medicine and has positive consequences for several persons (+, **see table 3**). Therefore, preference utilitarianism supports animal experiments if those experimental procedures are also performed on human beings. Unfortunately, Singer does not explain the difficulty in balancing the actual harm of testing creatures and the potential knowledge benefit for future individuals.

The second aspect comprises the probability or predictability of project knowledge. The project implementation of an animal study is more justifiable if retrospective reviews, similar studies, and the importance of the study content are examined so that the animal study will probably make a substantial contribution in a particular field compared to those projects that do not correspond to the above aspects. For this reason, the quality of knowledge displays a decisive factor for the vindication of animal studies. The quality of knowledge set up on past studies and therefore knowledge in the same area is dependent on these performed projects. The retrospective analysis can reveal if past planned study aims could be achieved or not. If many project goals could be reached, the probability increases for the prospective conclusion of the current study target (+, **see table 3**).

The third aspect is that the project objectives can be differentiated between local and global matters. In preference utilitarianism, all preferences play an equal role in the decision-making process as to whether an animal experiment should be granted, just because the benefits of animal experimentation affect individuals in proximity than those individuals who are geographically further away. Therefore, the broader distribution of preferences does not lead to more benefit, because the benefit, according to preference utilitarianism, is dependent on the number of preferences and

not on the distribution factor of preferences. According to preference utilitarianism, both local and global affairs should be considered equally whether an animal project should be approved (+, **see table 3**).

7.5.1.2. Practical benefit

The first aspect depicts the future aspect. There is a considerable probability that the practical benefit cannot arise from knowledge (scientific and extra-scientific reasons), which is why both the population, and the researchers would be frustrated by the strived preferences (bad consequences). For this reason, the practical benefit should not be given more weight in the ethical animal project evaluation compared to the knowledge benefit concerning the future aspect, because the practical benefit is always dependent on knowledge. Within the weighting process of the HBA, the practical benefits should be considered more important than knowledge itself. However, it is an indispensable circumstance to obtain scientifically tested knowledge to deduce potential practical benefits (+/-, **see table 3**). Otherwise, the practical benefit is unlikely to work as planned for the persons involved. For instance, a medical device must fulfill all theoretical aspects to work for the chosen area. Next, there must be enough material to produce the medical device in a huge amount for society. Therefore, it is important to note that practical benefits require solid knowledge. According to preference utilitarianism, the future aspect of practical benefits might have positive consequences for several persons if the knowledge quality is valid to deduce potential practical benefits.

The second aspect is the probability or predictability of the practical benefit. The project execution of an animal study is more justifiable and probable if retrospective reviews, similar studies, and the importance of the study content are examined so that the animal study will gain benefits for many individuals in a particular social area (maximize the quantitative preference realization) compared to those projects that do not correspond to the above aspects. However, it must be emphasized that the implementation of the project first generates evidence-based knowledge, with which the probability of a practical benefit can be estimated. Animal projects should not be permitted if the knowledge foundation contains a poor quality. The poor quality of knowledge leads to a worse probability assessment regarding the study goals (+/-, **see table 3**). For this reason, a continuous retrospective evaluation of a certain research area should be carried out to guarantee the quality of knowledge which will be used to assess the probability of achieving the practical benefits in animal testing projects.

The third aspect is that the project objectives can be distinguished between local and global matters. In preference utilitarianism, all preferences are classified as

equivalent (exception: vital versus trivial preferences) in the decision-making process as to whether an animal experiment should be granted, just because the benefits of animal experimentation affect individuals in proximity than those individuals who are geographically further away. For this reason, both local and global affairs should be treated equally (+/-, **see table 3**). In addition to that, Singer does not describe the difficulty in solving the problem between vital and trivial preferences. The difficulty consists of the balancing problem between a certain number of trivial preferences that can at some point be above a vital preference. However, Singer does not define a clear line between vital and trivial preferences. Indeed, preferences should be given more weight to those matters that, on the one hand, concern more individuals (and thus more preferences), or, on the other hand, if more vital preferences would be threatened, for example by diseases.

7.5.1.3. Secondary benefit

The first aspect displays the future aspect. Due to the principle of equality, the possible fulfilment of the wishes of personal or collective benefits (social or financial benefits, career, education, or reputation) cannot justify animal experiments (which are associated with killings and pains), because the vital preferences are more decisive than trivial preferences. For this reason, it is not permissible that the secondary benefits count more than vital preferences in the HBA whether an animal experiment should be carried out in a project. Especially, trivial preferences such as reputation or success tend to be context and time relative compared to the inviolable life of an animal or human being. Therefore, it does not matter whether secondary benefits will occur in the future or immediately on the same day (-, **see table 3**).

The second aspect is the probability or predictability of the secondary benefits. Due to the threat of vital preferences, the second aspect cannot justify animal experiments with sensitive beings (humans or animals). For this reason, there is no reasonable justification for preference utilitarianism, which would rank career goals, successes, reputational improvements, or financial reasons (trivial preference) higher than the life (vital preference) of animals. The justification to reject the animal project increases if the probability of the study builds up on a vague study design foundation (-, **see table 3**).

The third aspect is that preference utilitarianism makes no distinction between the performance of animal research projects in proximity or geographically remote localities concerning the possible secondary benefits. Hence, it makes no difference whether career goals, achievements, reputation improvements, or financial optimizations were generated locally or globally. It is therefore important that the ethical commissions do not make any difference in their project evaluations which populations or individuals will profit from the knowledge or practical benefits, because secondary benefits of animal testing can never justify this decision (-, **see table 3**).

7.5.1.4. Results

In preference utilitarianism, the following moral weight of the benefit concepts (knowledge, practical benefits, and secondary benefits) can be determined in the HBA. The decision-making process in ethical project evaluations should give positive moral weight to the knowledge benefit if the future aspect and the probability aspect (predictive value) are prognostic regarding the research purposes. In contrast, the localization aspect of project implementation does not play any moral role in the knowledge benefit assessment, whether an animal experiment is reasonably justifiable. However, the knowledge used from animal experiments is indeed morally relevant, whether this knowledge is going to be available, for example, for developing countries or industrialized countries. The decision-making process in ethical project assessments should give positive moral weight to the practical benefit if the future aspect, localization aspect, and the probability aspect (predictive value) are prognostically purposeful concerning the research aims. However, it must be stressed that the three aspects always depend on the established evidence of knowledge. Therefore, the practical benefits should never be considered and assessed in isolation in the HBA. The decision-making process in ethical project evaluations should give a negative moral weight to the secondary benefit, regardless of the future aspect, localization aspect, and the probability aspect (predictive value) (see also **table 3**). However, Singer does not delineate the difficulty in balancing the actual harm of testing creatures and the potential knowledge benefit concerning the vindication line between trivial and vital preferences. Therefore, the difficulty contains the balancing problem between a certain number of trivial preferences that can at some point be above a vital preference. Under which conditions can a vital preference be trumped by trivial preferences?

| Preference Utilitarianism | | | |
|---------------------------|-------------------|-------------------|-------------------|
| | Knowledge benefit | Practical benefit | Secondary benefit |
| Future aspect | + | +/- | - |
| Probability aspect | + | +/- | - |
| Localization aspect | + | +/- | - |

Table 3. The assessment of the aspect for the benefit concepts from the point of view of preference utilitarianism. +; positive moral justification for the benefit concept, -; negative moral justification for the benefit concept, +/-, the (positive or negative) moral justification depends on the performance.

7.5.2. Justification by Animal Rights View

7.5.2.1. Knowledge benefit

The first aspect is intended to take a closer look at the future aspect of knowledge. The possibility of carrying out animal experiments due to generating knowledge is possible if the animals are treated like humans with the principle of respect and acknowledging the inherent value. In addition, there must be no alternatives to animal testing. Therefore, it is allowed to test animals within a treatment procedure (blood collection for biomarkers, etc.). For this reason, it is conceivable in the animal rights view that knowledge can be generated from animal experiments if the inherent value of the animal is granted, and the principle of respect is applied too (+/-, **see table 4**). In contrast, it is unjustified for animals to be used for the epistemological interest of human beings because the inherent value and the principle of respect would be ignored. Regan differentiates the inherent value from the intrinsic and instrumental value. Both the instrumental and intrinsic values are actor-relative and situation-dependent, whereas the inherent value is independent of those factors. According to the animal rights view, animals are not allowed to be used for human study purposes of animal projects because the inherent value is shared by all individuals in the moral community and would be ignored if animals are used for instrumental or intrinsic values.

The second aspect is the probability or predictability of project knowledge. A possible substantial contribution in a particular field is also not relevant for the justification situation. The probability aspect would make the inherent value of a living being relativizable because it could be trumped by a probability occurrence of certain knowledge. However, the inherent value is independent of the actor and an absolute good, which is why it cannot be surpassed by statistical methods. Since the statistic plausibility does not solve the underlying problem of guaranteeing the inherent value of a living being, the probability aspect cannot serve as a valid justification for the performance of animal experiments and projects (-, **see table 4**).

The third aspect is that the project can be distinguished between local and global matters. For Regan and the animal rights view, everyone has the same moral rights, which is why regionality must not play a significant influence on the ethical project

assessments of animal testing procedures. Therefore, the location of knowledge benefit should not play a role in justifying animal experiments in the animal rights approach (-, **see table 4**).

7.5.2.2. Practical benefit

The first aspect sheds more light on the future aspect. The practical benefit is not a justification for carrying out an animal or human experiments if those experiments are only be performed for the potential practical benefit. The only exception is if the individuals agreed because this would consider the principle of respect and the inherent value. This applies to both the moral agents and the moral objects. The inherent value and the associated moral rights are shared by all individuals in the moral community. In the animal rights view, this is justified by the principle of non-harm, including moral objects, such as animals. For this reason, all individuals of the moral community should be protected from physical or psychological suffering and thus spared from an arbitrary suspension of scientific experiments. The possibility of performing animal experiments due to creating practical benefits is conceivable if the animals are treated like humans with the principle of respect and preserving the inherent value. Moreover, it is allowed to generate practical benefits within a treatment procedure (e.g. medical drugs, etc.). According to the animal rights view, it is possible that practical benefits can be derived from animal experiments if the inherent value of the animal is saved, and the principle of respect is applied as well (+/-, **see table 4**).

The second (probability or predictability) and third (local and global location) aspects can be dealt with the same reasoning of the animal rights view. According to the animal rights view, the ethical project evaluation of animal experiments is independent of the degree of probability and the question of location, because in both cases the inherent value and the principle of respect are diminished. An animal experiment is not allowed to be performed because it is believed that a more probable practical benefit can be generated from a certain animal experiment compared to another practical benefit (-, **see table 4**).

7.5.2.3. Secondary benefit

According to the animal rights view, all mentioned aspects can be summarized below, because the argumentation is the same in all cases. As discussed earlier, both moral agents and moral objects have an inherent value. For this reason, all individuals in the moral community have the same moral rights. Therefore, the reasons for career goals, successes, reputation improvements, or financial optimizations are not a justification for obtaining a positive ethics evaluation for the conduct of animal or human experiments. Of course, the future, probability, or local aspect may lead to a better reputation for the researcher or the research institution if the research impact is greater, but these secondary benefits are not allowed to ethically justify the performance of an animal experiment according to the animal rights view (-, **see table 4**).

7.5.2.4. Results

According to the animal rights view, the following moral weight of the benefit concepts (knowledge, practical benefits, and secondary benefits) can be determined in the HBA. The decision-making process in ethical research assessments should give positive moral weight to the knowledge benefit or practical benefit if the future aspect considers the inherent value and the principle of respect for all animals. The benefits may arise within the treatment procedure of the animal. Otherwise, the decision-making process in ethical project evaluations should give a negative moral weight to the knowledge if the future aspect, the localization aspect, or the probability aspect (predictive value) shall be sufficient for the justification, just because of the desire to perform animal experiments to gain knowledge for a human, an animal, or the environment.

The decision-making process in ethical project assessments should give a negative moral weight to the practical benefits (except the future aspect) and secondary benefits (**see also table 4**). Importantly, the future, probability, or local aspect may generate a better reputation for the researcher or the research institution, but these secondary benefits cannot serve as an appropriate justification for the allowance of animal experiments or projects.

| Animal Rights View | | | |
|---------------------|-------------------|-------------------|-------------------|
| | Knowledge benefit | Practical benefit | Secondary benefit |
| Future aspect | +/- | +/- | - |
| Probability aspect | - | - | - |
| Localization aspect | - | - | - |

Table 4. The assessment of the aspect for the benefit concepts from the point of view of the animal rights view. +; positive moral justification for the benefit concept, -; negative moral justification for the benefit concept, +/-, the (positive or negative) moral justification depends on the performance.

8. Answer to the research question

In this master's thesis the following research question is answered: Can it be justified to prioritize practical benefits over knowledge gains in the harm-benefit analysis within the framework of the animal rights view or preference utilitarianism? Therefore, the Brønstad benefit classification system in animal research was delineated **(6)**. Brønstad benefit classification system distinguishes benefits into primary and secondary benefits. Here, primary benefits are served as crucial evaluation tools in the HBA of animal projects. In contrast to that, secondary benefits are not allowed to justify the authorization of animal experiments. Primary benefits comprise knowledge benefits (information, skills, understanding, etc.) and practical benefits (therapies, conservation, etc.). Secondary benefits encompass individual and collective career benefits, success, money, etc.**(6)** At next, I analyzed the passage of the EU Directive 2010/63/EU to determine relevant linguistic expressions for answering the research question. The EU Directive 2010/63/EU contains the necessary performance of the HBA for the competent authorities in all European Member States before the animal experiment can be carried out. The competent authorities have to assess expected harms (suffering, pain, and distress) on animals and weigh these harms against the potential benefits for humans, animals, or the environment.**(3, 5)** In particular, the HBA project assessment contains the following passage: “the HBA of the project, to assess whether the harm to the animals in terms of suffering, pain, and distress, is justified by the expected outcome taking into account ethical considerations, and may ultimately benefit human beings, animals, or the environment” **(3, 5)**. For this reason, I focused on the following terms of the previous passage in more detail: “ultimately benefit” and “ethical considerations”. The terminology in the HBA is of great importance because the competent authorities have to discuss the expected harms and potential benefits and find a final decision for the respective animal project. Therefore, the significance of the HBA evaluation for the research question is that a precise comprehension of the linguistic terms used facilitates the communication and discussion in animal research. Hence, the linguistic expression benefit has to be explained in the EU Directive 2010/63/EU passage “ (...) ultimately *benefit* human beings, animals, or the environment (...) **(3, 5)**” to get a more precise comprehension of the balancing process between expected harms and potential benefits in the HBA. Furthermore, the linguistic expression ethical consideration in the phrase “ (...) the harm to the animals in terms

of suffering, pain, and distress, is justified by the expected outcome taking into account *ethical considerations* (...) **(3, 5)**" of the EU Directive 2010/63/EU has to be assessed to identify applicable ethical standpoints in the HBA. Therefore, Peter Singer's preference utilitarianism and Tom Regan's animal rights view were used to generating suitable arguments and reasons for the ethical discussion within the HBA evaluation process. Peter Singer's preference utilitarianism and Tom Regan's animal rights view were used to vindicating the comparison between the expected animal harm and the potential benefits in animal projects.

According to preference utilitarianism, the decision-making process in ethical project evaluations should give positive moral weight to the knowledge benefit if the future aspect and the probability aspect are prognostically concerning the research aims. In contrast to that, the localization aspect of project evaluation does not play a moral role in the knowledge benefit assessment, whether an animal experiment is reasonably justifiable. In addition to that, the decision-making process in ethical project evaluations should give positive moral weight to the practical benefit if the future aspect, localization aspect, and the probability aspect are prognostically purposeful regarding the research aims. It is important to stress that the three aspects always depend on the established evidence of knowledge. Hence, the practical benefits should never be considered and assessed in isolation in the HBA. Besides, the decision-making process in ethical project evaluations should give a negative moral weight to the secondary benefit, regardless of the future aspect, localization aspect, and the probability aspect, because personal reputation improvement or financial gain should not justify the performance of animal experiments according to the preference utilitarianism.

According to the animal rights view, the decision-making process in ethical research assessments should give positive moral weight to the knowledge benefit or practical benefit if the future aspect takes into account the inherent value and the principle of respect for all animals. This is since the benefits may arise within the treatment procedure of the animals. Apart from that, the decision-making process in ethical project assessments should give a negative moral weight to the knowledge if the future aspect, the localization aspect, or the probability aspect shall be sufficient for the justification, just because of the effort to carry out animal projects to increase knowledge for human, animal, or the environment. Moreover, the decision-making process in ethical project assessments should give a negative moral weight to the

practical benefits (except the future aspect) and secondary benefits. Of note, the future, probability, or local aspect could create a better reputation for the researcher or the research institution, but these secondary benefits cannot serve as an appropriate vindication for the allowance of performing animal experiments or projects.

The above-mentioned facts of the research answer led to the following conclusion: Both Peter Singer's preference utilitarianism and Tom Regan's animal rights view to prioritize the knowledge benefit compared to the practical and secondary benefits regarding the future, probability, and local aspect. Furthermore, the weight of the practical benefits always depends on the knowledge quality. In addition to that, secondary benefits should not play a role in the ethical project evaluation, because personal reputation enhancement or financial gain should not be prioritized compared to animal lives. Nonetheless, the personal reputation may increase if the researcher develops a vaccine after an animal project. However, the researcher's intention to become more famous is not allowed to be a suitable argument to perform an animal experiment or project.

9. Summary

Until now, humanity has used many experimental animals in science to optimize human knowledge and practice in medicine. In recent times, the awareness and consideration of people for animals and experimental animals has grown. The European Union's response was to introduce the EU-Directive 2010/63/EU. Therefore, the competent authorities of all Member States of the European Union must carry out the HBA to obtain a positive ethical decision for research projects with animals. The HBA serves to balance the expected harms on animals with the potential benefits. The benefit concepts in the HBA have hardly been treated and evaluated. For this reason, an extensive literature search was carried out in the database "PubMed" to analyze the original articles. Consequently, an ambivalence was found between the knowledge and practical benefits. This ambiguity was illustrated by the measles vaccination example. This example had shown that knowledge benefits and practical benefits can be beneficial and interact with each other in reality. The moral justification of the benefit concepts was evaluated by Singer's preference utilitarianism and Regan's animal rights view. The preference utilitarianism and the animal rights view approach weighed the reasoning of the benefit concepts in the ethical evaluation process of animal testing procedures. Moreover, modulating factors were being examined as to whether they can influence the weight of benefit concepts and thus the justification of the benefit concepts.

The research results of the literature search and the assessment of the benefit concepts with the ethical positions can be summarized as follows: According to the preference utilitarianism, the decision-making process in ethical project assessments can give greater weight to the knowledge benefit if the future aspect and the probability aspect are prognostically useful concerning the animal research aims. In contrast, the localization aspect of project implementation does not play any moral role in the knowledge benefit assessment. The decision-making process in ethical project assessments gives greater weight to the practical benefit if the future aspect, localization aspect, and the probability aspect are prognostically expedient regarding the research targets. However, it must be emphasized that the three aspects always depend on the evidence of knowledge. The decision-making process in ethical project evaluations gives a lower weight to the secondary benefit, regardless of the future aspect, localization aspect, and probability aspect.

According to the animal rights view, the decision-making process in ethical research evaluations gives a higher weight to the knowledge benefit and practical if the future aspect considers the inherent value and the principle of respect of all animals. Otherwise, the decision-making process in ethical project evaluations gives a lower weight to the knowledge and practical benefit concept concerning the future aspect, the localization aspect, and the probability aspect. The decision-making process in ethical project assessments gives a lower weight to the secondary benefit, regardless of the future aspect, localization aspect, and probability aspect.

The research transparency, reporting habits, the methodological-statistical approach of the research design, the responsibility (researchers, reviewers, and journals) as well as the maintenance of scientific standards (external, internal, and constructed validity) and the publication of all study data could be explored as modulating factors to increase the justificatory power of the respective benefit concepts in the HBA.

10. Discussion

For the first time, the applicable benefit concepts of the HBA were evaluated and the ethical consideration of projects with animal experiments was analyzed.

Therefore, two important passages of the EU Directive 2010/63/EU were picked to explore the role of HBA weighing performances in animal research evaluation processes. The first passage includes the phrase “(...) ultimately *benefit* human beings, animals, or the environment (...) **(3, 5)**”. So far, the term benefit was not clearly defined in the HBA. However, the term benefit is essential for the HBA process to weigh the potential benefits against the expected harms on animals. In addition to that, the conceptualization of benefits in the HBA was explored by using Brønstad's benefit classification system.**(6)** The second passage comprises the phrase “(...) the harm to the animals in terms of suffering, pain, and distress is justified by the expected outcome taking into account *ethical considerations* (...) **(3, 5)**”. Another crucial aspect of the HBA is to determine applicable ethical positions. Therefore, the preference utilitarianism and animal rights view was used as ethical justifications for the respective benefit concepts in the HBA to generate suitable arguments. These reasonings support the final approval of the competent authorities whether a certain animal testing procedure or project can be performed. The Brønstad benefit classification system **(6)** was used in the analysis process, because of the suitable benefit concepts (primary and secondary benefits) which guaranteed that each benefit could be assigned to one of these benefit concepts. In addition to that, the benefit concepts (primary and secondary benefits) facilitated a comprehensible comparison between the findings in the articles found on the PubMed database.

Scientific progress is essential for improving the quality of life by enabling better therapeutic interventions, technical aids, or more environmentally-friendly lifestyles. However, this also requires ethical accountability of researchers, committee members, and the entire population, so that the potential benefits are not transformed into disadvantages for humans, animals, or the environment. The anticipated benefits are exceedingly difficult to predict and have a different impact in the various research areas. To increase the likelihood of expected benefits, model selection, study design, staff experience, and transparent reporting of results should be optimized. For this reason, the ARRIVE Guidelines were introduced in 2010 to maximize reporting quality in *in vivo* research.**(133)** Graham also explained the point that scientific progress can

be achieved by increasing substitution of animal experiments by cell technologies, 3D tissue construction, bioprinting, organ-on-chips, microfluids, *in vitro*, or *in silico* methods. In addition, knowledge is essential so that both the concepts of harm and the anticipated benefits can be reasonably planned and tracked.**(76)** For this reason, surveys must be conducted to survey and analyze the different opinions and disfigurements on this subject.

Perel and colleagues emphasized that it is essential to plug the "gap" between animal trials and clinical trials by providing systemic reviews and increasing awareness of different research biases (publication bias etc.). Data processing of results in animal studies allows a more optimal search concerning animal models for one's research, why a well-established data register could be a favorable tool for future research purposes. An established register could make the results between animal trials and clinical trials more comparable in the future. The "data mining" could serve as a key tool for a serious retrospective evaluation of animal research and clinical research. This factor allows more efficient medical cures and comparisons between animal and clinical trials. It can also be explained to the public in a comprehensible way, thereby increasing confidence in research and implementing it at a political level, so that institutions can provide financial support to the fields of research.**(72, 75)**

According to Bressers and colleagues education, governmental influence, and data sharing are the three pillars to implement animal-free innovations in animal research fields.**(135)** Grimm and colleagues stated that the HBA should be substituted for prospective project evaluation by a harm-knowledge-analysis. Another crucial aspect is the need to discuss whether a certain knowledge should benefit the current population or only equip future generations with certain knowledge. This requires an argumentative clarification of the rationale with which future people and societies do not play an essential role, as opposed to living individuals.**(88)**

In preference utilitarianism, the knowledge benefit receives both a positive moral justification for itself and a positive moral justification for the practical benefit concept. Furthermore, the moral acceptance of the practical benefits in the HBA has also been clearly emphasized. Preference utilitarianism also takes future preferences into account, which is why current and future people play a role in the decision-making process. The same conclusion can be drawn from the findings of the animal rights view because future existing individuals should also be given the same moral rights. However, the moral justification for animal experiments is more difficult to

justify. After all, if the inherent value and the principle of respect are maintained, it must not be misused for research interests.

The final points are the pleasures or frustrations, which are an essential part of a research person. Pleasure and contemplation are just as crucial for Tannenbaum, as practical benefits. He also emphasizes that much of what is being researched has no direct application in mind. This lifestyle science just wants to expand the knowledge boundaries that are driven by personal pleasures. Scientific research needs a subjective curiosity about a certain topic. However, the author emphasizes that this aspect does not explain the justification why and at what point knowledge can justify certain research projects.**(29)**

According to preference utilitarianism and animal rights views, Tannenbaum's argumentation is morally not acceptable. The curiosity-driven researcher should not have permission to perform each (animal) experiment, just because it would satisfy his/her interests and pleasures. On the one hand, the vital preferences of the animals are completely ignored (preference utilitarianism) and on the other hand, the inherent value (animal rights view) of moral members is relativized and destructed. For this reason, the "spin-off argument" must be rejected, because both the uncertainty of practical and knowledge benefits and the possible first step of a research objective, should not be classified higher than the inviolable life of animals.**(29)**

The next point of discussion is the influence of the population on the decision-making process of animal experiments. In the second step of his checklist, Stafleu mentioned economic interests, which will be subsumed under the interests of knowledge and health. He is aware of the fact that economic aspects are decisive for scientific research areas, since the personnel, the materials, temporal, and spatial conditions demand a lot of financial loss, but in animal research, the intrinsic value of animals should not be compared with monetary factors.**(2)** In another study, Lund sent out a questionnaire to the Danish population and was able to find three different attitudes to animal experiments. In total, there were 12,131 questionnaires (sample 1: 5311 and sample 2: 6820), of which 2,358 (sample 1: 1247 and sample 2: 1111) were partially or completely answered and with which further analyses were carried out. The survey identified three groups that can be divided into approvers, disapprovers, and reserved.**(84)** Hagelin found that context-specific factors can modify individual attitudes to animal testing.**(136)** In his surveys, Lund was able to identify three factors that were

decisive for the above groups. The purpose of the research (safety or medicine, obesity, migraines, cardiovascular disease, or cancer), the pain level, and the animal species. The three factors were weighted differently in the three groups. For example, the research purpose is the most important factor for the approvers (46.5% of 1247), whereas the pain level for the disapprovers (52.6% of 1247).**(84)**

The measles vaccination example showed that practical benefits do not need to be accepted by the population. This can also be supported by extra-scientific factors (market availability, production performance, etc.). For this reason, it is justifiable that the population should have a participation in whether certain practical benefits should be sought through scientific research processes. The more the research objectives are accepted by the population, the more these objectives are used and integrated into society. In contrast, the vaccination example was able to demonstrate that the population cannot reasonably judge evidence-based knowledge. For this reason, it is not permissible for the population to decide whether to classify knowledge as scientifically proven. Evidence-based knowledge must be able to meet the criteria, objectivity, reliability, and reproducibility. These findings cannot be influenced by populations. Furthermore, the population is accused of misleading causality between animal projects and of applicable research results because each research project entails inherent methodological and practical uncertainty, why society's confidence in science is becoming increasingly depleted. Moreover, the idea that the raw data of research projects must be applied in certain areas means that the responsibility of the researchers is beyond their scope. Scientific projects should be evaluated according to their quality of research and contribution in their respective research field. Moreover, science cannot confirm or verify itself through practical benefits, because otherwise, it would render these benefits meaningless.**(71)**

HBA implies that the value of research exists only if practical benefits arise, but which cannot be offered or guaranteed by the knowledge of science. The current formulation of the HBA leads to a loss of credibility in research towards the population. The perceived benefits support an inverse relationship between benefit and risk. There is also the possibility that the moral objection may be weighed against the perceived benefits concerning applications. The simple data from studies only show a certain raw material that does not yet have to have any practical use. In addition, a single study cannot yet generate a practical benefit, but only several studies within a field of research can do so.**(3, 9)**

The HBA definition includes the passage “outcome and may ultimately benefit (5)” which implies that both the outcome and the benefit have a common linguistic because otherwise, this would result in the legitimization of a procedure that could evaluate the outcome independently of the respective benefits.(71) Another passage is “may ultimately benefit (5)” which means that the outcome must lead to a potential benefit in a certain period. The justifiable power of practical benefits is defined by the respective timeframe and the probability of realization. The questions of when what, how, and who are in the foreground, so that the justification can be checked regarding time frame, field of research, group of people, and methodology. The authors argued that the foundation is formed by knowledge and knowledge can be further explored. Therefore, a clear line between the various fields of research cannot be drawn exactly.(88) Eggel and colleagues formulated three criteria for a reasonable HBA: 1. proof that the project may ultimately *benefit* humans, animals, or the environment 2. prospective qualification of the outcome with regards to its potential and expected benefits 3. prediction of the likelihood and time frame of achieving the benefit. The above criteria would have to be set by the political level for valid societal benefits and be subject to a check as to whether the respective research objectives can be achieved with animal experiments or projects. The use of possible research results and their application areas also depends on the factors market, profitable production, and efficient distribution (“extra-scientific factors“).(88)

It is also worth pointing out that both the HBA and the freedom of scientific research must not be dominated on a political level for financial reasons. The activities of research are protected as a basal right to freedom in the constitution. The freedom to choose topics and methods is derived from this constitutional law. However, that right cannot in any way have unlimited validity. Therefore, restrictions are necessary if fundamental values should be violated in the research process. Therefore, research projects involving animal intervention should have a basis for legitimacy. This basis of legitimacy can be defined in politics.(137) However, political participation in scientific research is just as important as funding programs and legal regulations can facilitate the implementation of research projects. In addition to that, policy measures and clarification actions can optimize communication between the population and the practicing researchers.(82)

Grimm and colleagues discussed the point that the value of knowledge as a scientific outcome is a necessary but insufficient condition for societal benefits since an interpretative performance is indispensable for a particular field of application. The quality of knowledge and answering the questions “What will be the benefits of the work?”, “Who will benefit from the work?”, “How will they benefit/impact?” and “When (where possible) will the benefits be achieved?” represent two different perspectives on how to justify an ethical project evaluation. The authors argue that knowledge is a necessary foundation, and the practical benefits refer to it. For this reason, the question arises as to whether a particular knowledge in a certain field of research that will be accessible soon, can be considered as more important than possible knowledge in the distant future. Therefore, a line between the different research fields cannot be drawn clearly, because several research areas benefit from each other and are interconnected.**(88)**

In his paper, Tannenbaum presents the knowledge justification by analyzing five elements of the knowledge concept. So far, there is no agreement in the literature, what should be understood by the term knowledge, and hence no clear stringency and unity can be achieved in ethical committees. He stated five elements: factual knowledge, experiential knowledge, contemplation, intellectual activities, and pleasures/frustrations. As a factual knowledge, he understands pure information, facts, or explanations of certain scientific topics, why this kind of knowledge is called “propositional knowledge”.**(29, 138)** The experiential knowledge is available only to sagacious experts since only these individuals have the corresponding wealth of experience and can therefore better assess certain subjects. The third element is contemplation, which examines the possible facts or information of a study on current and prospective facts, explanations, and theories. The question arises if a certain knowledge is to advance the entire understanding of a research area or not. Tannenbaum defined intellectual activities as intellectual faculties or skills that can also be generated from the knowledge and may be important for researchers to carry out animal researches.**(29)**

The second decisive concept of benefit in animal research for humans is the practical benefit concept that has a certain scope in society. An essential point is that some research fields (applied research, food research, etc.) can offer more obvious applications than, for example, basic research. However, it must be stressed that applied research can benefit from the knowledge of basic research and can often build

on its derived conclusions. Now, the challenge is that potential benefits in animal testing must be accurately identified and predicted to perform a reasonable HBA. The prospective human benefits can diverge in different countries in terms of socio-economic, environmental, sanitation, and health conditions. Therefore, the population conditions must be considered so that the research purposes are not ineffective but can also be used by most of the society.**(82)** For this reason, the factors of the practical benefit concept and their basis of justification must be depicted, and their criticisms are explained. Grimm and colleagues mentioned that “societal benefits” may bring perceivable positive consequences to humans, animals, or the environment. But the problem is that the anticipated prospective societal benefits are considered impossible to predict.**(71)**

Therefore, the following questions warrant further study in animal research: "What knowledge can humanity reasonably dispense with?" or "What influence should the population have on the assessment of the benefit concepts in the HBA?". In the literature, the effects of secondary benefits within the project evaluation process of animal experiments have hardly been dealt with. For this reason, the secondary benefits must be subjected to a more detailed analysis.

11. Implication for scientific research

The research results reveal several implications for animal research conduct. The first implication is that knowledge has a dual character. On the one hand, the knowledge benefit serves as reasoning for whether an animal experiment can be carried out. On the other hand, it is a necessary condition that the research designs, research objectives, and research intentions should be based on scientifically proven knowledge. The aim is to increase the likelihood that the knowledge benefits or practical benefits of animal testing procedures can be achieved. Bout et al. underlined that the probability aspect should be integrated within the HBA weighing process to make the knowledge or practical benefit occurrence more probable **(83)**. The assessment of probability is a necessary condition whether a research project with animal experiments is allowed to be performed at all. After the probability has been estimated as high, the HBA can be performed in the next step. If the probability of realizing a practical benefit or a knowledge benefit is very uncertain in advance, then the ethical acceptance of the animal experiment is not justified. The same reasoning can be made with the knowledge aspect. If there is no existing knowledge or the knowledge makes another research conclusion more reasonable, then animal testing should not be justified. For this reason, it is conceivable that evidence-based knowledge should be used as a premise to carry out the HBA as the next step. Thus, the dual character of knowledge is important because knowledge must be evaluated in terms of importance and originality in a certain research field, before performing the animal experiment or project.

12. Abbreviations

ARRIVE Animal Research: Reporting In Vivo Experiments

GSPC Gold Standard Publication Checklist

HBA Harm-benefit analysis

ICLAS International Council for Laboratory Animal Science

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14. Figures

Figure 1. Flow chart of article selection and inclusion. Adapted from (70)..... **33**

Figure 2. The differentiation in articles of the PubMed database is displayed following the Brønstad benefit classification system (Figure 2A). Furthermore, we divided the primary benefit into knowledge and practical benefit categories (Figure 2B)..... **41**

15. Tables

| | |
|---|-----------|
| Table 1. Key search strings (Adapted from (68))..... | 34 |
| Table 2. All advantages are cited that can be translated into benefits. | 39 |
| Table 3. The assessment of the aspect for the benefit concepts from the point of view of preference utilitarianism. +; positive moral justification for the benefit concept, -; negative moral justification for the benefit concept, +/-, the (positive or negative) moral justification depends on the performance. | 57 |
| Table 4. The assessment of the aspect for the benefit concepts from the point of view of the animal rights view. +; positive moral justification for the benefit concept, -; negative moral justification for the benefit concept, +/-, the (positive or negative) moral justification depends on the performance. | 63 |