



Department of Political Science
Major in Politics, Philosophy and Economics

Chair in Bioethics

**The Ethical and Moral Status of Invasive Animal Research: The
Dilemma and Alternative Approaches**

Supervisor

Prof. Daniele Santoro

Candidate

Livia Di Salvo

ID Number 074182

Academic Year 2015-2016

“In the agony of death a dog has been known to caress his master, and everyone has heard of the dog suffering under vivisection, who licked the hand of the operator. This man, unless the operation was fully justified by an increase of our knowledge, or unless he had a heart of stone, must have felt remorse to the last hours of his life”

Ann Druyan, Carl Sagan (1993)

Table of Content

Abstract	Page 4-11
Introduction	Page 12-13
1. The Context of The Debate	Page 13
<i>1.1. The Case in Favor of Animal Experimentation</i>	Page 13-14
<i>1.2. The Case Against Animal Experimentation</i>	Page 14-15
<i>1.3. The “Middle-Ground” Position</i>	Page 15-16
<i>1.4. The Three Different Positions of the Moral Status of Animal Experimentation</i>	Page 16-18
<i>1.5. The Correlation Between Moral Status and Morally Relevant Features</i>	Page 18
<i>1.5.1. Sentience</i>	Page 18-19
<i>1.5.2. High Levels of Cognitive Capacity</i>	Page 20
<i>1.5.3. The Capability to Flourish</i>	Page 20-21
<i>1.5.4. Sociability</i>	Page 22
<i>1.5.5. Possession of Life</i>	Page 22-23

1.6. <i>The Reality of Animal Pain</i>	Page 23-24
1.6.1. <i>Pain: An Evil in Itself</i>	Page 24-25
1.6.2. <i>The Equality Principle</i>	Page 25-26
1.6.3. <i>The Justification Principle</i>	Page 26-27
1.6.4. <i>The Value Principle</i>	Page 27-28
2. The Main Forms of Animal Experimentation	Page 28-29
2.1. <i>From the Past to the Present: Early Forms of Animal Research</i> ...	Page 29-31
2.2. <i>Cognitive Behavioral Research</i>	Page 31-32
2.2.1. <i>Common Area of Behavioral Research: Drug Addiction and Abuse</i>	Page 32-33
2.2.2. <i>Common Area of Behavioral Research: Maternal Deprivation</i>	Page 33-34
2.2.3. <i>Behavioral Research: Diseases that Affect Emotion and Behavior</i>	Page 34-35
2.3. <i>Genetically Modified Animals: Gene Modification</i>	Page 35-37
2.4. <i>Research in the Pharmacology Industry</i>	Page 37
2.4.1. <i>Toxicity Testing</i>	Page 38-39

2.4.2. <i>Cosmetic Testing</i>	Page 39-41
3. The Way Forward: Meeting the Challenge	Page 41-42
3.1. <i>Wasteful and Unreliable Experiments</i>	Page 42-44
3.2. <i>Alternatives to the Problem of Animal Testing</i>	Page 44
3.2.1. <i>Epidemiology Studies</i>	Page 44-46
3.2.2. <i>In Vitro Testing</i>	Page 46
3.2.3. <i>Computer (In Silico) Models</i>	Page 47-48
3.2.4. <i>Autopsies and Biopsies</i>	Page 48
3.2.5. <i>Research with Human Volunteers: Clinical Studies</i>	Page 49-50
3.3. <i>EU and US Legislations on Animal Experimentation</i>	Page 50-51
3.3.1. <i>The Principle of the Three Rs</i>	Page 51-53
3.3.2. <i>The Problem with the Three Rs' Principle</i>	Page 53-54
3.3.3 <i>Lack of Research Transparency and Public Awareness</i>	Page 54-55
Conclusion	Page 55-57
Bibliography	Page 58-62
Abstract (in Italian)	Page 63-71

Abstract

The ethical and moral status of invasive animal research is what sparked the need for change and the need to move towards a vision far from the classic need for traditional methodologies to be carried out in scientific laboratories using animals as models for human disease. This is because animals have commonly been used as models to mimic human disease in the field of basic and biomedical research and as subjects for the testing and development of new drugs, vaccinations, cures and preventions to common diseases as to advance and improve medical knowledge and human health. Indeed, since the start of animal experimentation, which dates back to Ancient Greece, medical research has indeed been an essential field for widening the range of knowledge regarding human health and diseases, even in regards of basic learning processes, like thirst, hunger or reproduction, along with essential information regarding the sensory processes: hearing, taste, vision, and pain perception. The range of research fields covered by animal testing has increased tremendously since the 1950s, when new procedures were adopted as diseases and rare illnesses were starting to infect human populations. Cognitive studies conducted on animals have provided both an ecological and comparative perspective upon issues of the mind and intellect. While other experimentations, provided information on how both levels of cognition and sensory functions can depend on previous life experiences. Animal research has provided with knowledge on the modes of adaptation to changes, along with development, to all types of learning, and evolution, allowing identification and refinement of the main behavioral principles throughout which the creation of efficient methods for self-reliance and promoting learning was achieved. It has been essential in understanding behaviors affected by environmental toxicants and psychoactive drugs, allowing a better comprehension of physical dependence and drug abuse. Through animal studies, treatment for drug dependence and disorders, like for example depression, anxiety and schizophrenia, have been created. Yet, notwithstanding the importance of science and medicine being fields of worthy causes, animal experimentation has relied in experiments subjecting animals to high degrees of pain,

suffering and distress, as well as reducing the quality of their lives. This is because up until today, animal experimentation has reached procedures of invasive kind, where animals are subjected to environment, behavior, and health manipulation, in most cases them being exposed to artificial diseases found in humans. The extended number of animals used and killed after and during testing, the invasiveness of the procedures, the inhumane treatments, the high degree of pain and suffering that the animals are exposed to, along with the deprivation of their natural environments and wildlife, has led to an increase in awareness and intense debates regarding the ethicality and morality of practicing invasive experimentations on animals, such as its necessity, acceptability, justification and the reliability and effectiveness of the research findings. In fact, the ongoing debate on the matter about the ethics of animal experimentation has mainly focused on three potential, complex and different positions: “in favor”, “against” or in-between, known as “the middle-ground” position. These positions focus on the ethical dilemma of whether humans have the right to use animals and inflict them terrible pain for medical purposes, especially when history has proven that not all experimentations can be fully reliable, guaranteed to be successful, and where human benefits do not justify the harm caused to animals. Analyzing the three different positions, two main questions to the debate arise: firstly, “does the use of animals in the field of medical and scientific research provide with valid, relevant and useful results and knowledge (and that cannot be achieved otherwise)?” and secondly, “should it be morally acceptable and permissible for humans to cause extensive pain, suffering and death to animals as to obtain aims that mainly benefit the human community? In order to consider and analyze the given questions one must first explore the different complex issues raised by testing on animals, such as the argumentation regarding the moral status of human and non-human animals along with the degree of pain, distress and suffering experienced by the subject of the experimentation. The debate, is often reduced to the question of the definition of the moral status, along with its moral importance, in relation to humans and non-human animals. In respect to the moral status different views and positions can be identified: the first placing humans at the top the moral hierarchy as it is

believed that they possess some morally vital property that instead all other non-human animals lack (this view is mainly supported by those who are in favor of animal experimentation); the second focuses on the idea that even if humans may be morally superior, they should have the moral duty to protect, care and feel compassion towards the “lesser” creatures rather than using them as tools for furthering human knowledge; and thirdly there is the position (mainly supported by those against animal experimentation) which places no categorical distinction between species, giving them the same level of moral status and thus categorizes a classification of moral distinction to be insufficient as to explaining the justification of animal use. For those under this position it is just a moral wrong to subject any animal to experimentation and unfair treatment, as it would be unacceptable if done to a human being. This view basically claims that if experimentation is carried out on animals and recognized as acceptable in order to achieve knowledge in research, then it would be acceptable and justifiable to do so also on humans, due to their equal moral status. Nevertheless, neither three views answer the question of the permissibility and validity of using animals for scientific and medical purposes. What is essential, thus, is to understand what are the morally relevant features that characterize a human and a non-human animal in order to be classified as being a moral subject (and thus comprising of a moral status) as to understand how animals should be treated in research experimentations and otherwise. This is because the appropriate moral care of a being should not just depend on the species to which the subject belongs to but to the moral characteristics and features it possesses as relevant features provide with a sense of reason for moral apprehension, where animals having at least one or all features should be retained to be moral subject, and thus human interference with one of these features should require careful and precise justification when infringed upon it. It is thus essential to take the following features as relevant in order to understand how to make and take into account moral decisions in respect to the moral subject these being sentience, high levels of cognitive capacities, the capability to flourish, sociability and the possession of a life. After assessing the question of moral status and the relevant features attributed to a moral subject, it is essential to further the understanding of the ethical

implications of animal testing in regards to the nature and reality of pain (it being a fundamental evil), distress, and suffering that animals experience with the invasive procedures they are exposed to as to explain pain in relation to animal experimentation. Nonetheless, it can be said that these ethical and moral issues, that have arisen in relation to animal experimentation, have been essential tools for further shaping legislation across Europe and the United States, also by giving birth to many organizations and institutions aimed at protecting animals in laboratories, aimed at tackling down the vast variety of different forms and procedures of experimental research conducted on animals. These forms of experimentation, in fact, fall under a wide range of research categories. One of these being cognitive behavioral research aimed at understanding both the mind and behavior of human and nonhuman animals in order to advance the welfare of humans, these being conducted, to list a few, on the hearing, vision, thirst, hunger, reproduction, fetal development, perception of pain, stress, aggression, fear, maternal deprivation, drug abuse along with cigarette and alcohol dependence. Gene modification research, instead, is another invasive research field based on researchers speeding the mutation process in animals with the process of chemical mutagens and irradiation, increasing greatly the ability to study and manipulate genomes of animals in order to develop gene-detecting technologies, and understand fully the function and structure of the different human and non-human genes. Nevertheless, by injecting human disease or by gene modification, the animal models manipulated not only go through invasive, stressful and painful procedures, but are also likely to conduct lives full of health problems and high chances of increased lethality. Animal testing has been a key element also in the pharmaceutical field, for the process of development, discovery and production of new pharmaceutical products, as well as cosmetics and toxicology testing. Pharmaceutical industries test medicines and products on animals in order to ensure the safety of the product and the efficacy in treating a disease or condition, even if animal testing does not ensure a product's safety for consumers as animals have showed to react differently to some products compared to humans. Products, before being approved, released, and tested on consumers, are first tested on animals in order to

assert the toxicology of the product and its possible side effects. Nevertheless, these experiments have been proven inadequate, as animals not always responded to substances of addicting kind like humans did, causing no fundamental insight into the causes of self-destructing behavior or of drink addiction, and thus do not guarantee effective treatments for humans. All this underlined even more the fact that, even if animal models did appear to be reliable and adequate subjects for testing, they provided with uncertain data as there would always be some other factor or condition that would alter the research findings (because of uncertainty variables). In fact, the real question of invasive animal procedures lies in whether the different types of experimentations conducted on animals are useful for improving human health and knowledge, or just wasteful and unreliable. Some believe and argue that even if it is wrong to unnecessarily abuse and inflict pain on animals, that the experimentation must continue as animal models provide important scientific resource. But the reality of animal experimentation is that most of the experiments conducted do not contribute in improving human health and diseases, as many medical treatments developed in animals rarely translate to human beings, and diseases which are artificially produced in animals in laboratories, are never identical to those that take place naturally in humans. This is because many animals and humans are different biologically in many substantial ways, and thus the results obtained in animals will not yield and mirror the results that can be correctly applied to the human conditions. The unreliability of animal testing's finding, due to the various factors which do not ensure fully reliable results, has pushed scientists to adopt and address new alternatives to animal experimentation, not only to decrease the number of animals used, but also to increase the efficiency in research findings as to improve human health, medical knowledge and animal welfare. Through the numerous technological advances made in the field of medicine and research, new methods for testing have been created as alternatives to the classic methods. In fact, human epidemiological and clinical studies, human vitro studies on human cells and tissue methods, high-level human patient simulators, cadavers, computational models, are potentially alternative methods to research. These alternatives have proven to be

more reliable, precise, faster and even less expensive, but especially they are humane alternatives to testing animals for the advancement of medicine. These models show that human well-being and health can still be obtained and promoted by adopting different sophisticated and nonviolent methods and approaches of investigation and prevention of disease, by also embracing ethical science. With the introduction of these new alternatives, changes in medical and research attitude are slowly taking place. Reducing the number of animal used and enforcing controls on test conducted throughout new legislations, regulations and policies proposed and passed mainly by the European Union and the United States, highlight the start of a new push towards global efforts as to encourage the progressive transition away from having to use animals in laboratories, especially when non-invasive, effective and reliable alternatives exist. Legislations enacted aims at strengthening and improving animal's welfare by anchoring to the concept of the "Three Rs" (Replacement, Reduction and Refinement), integrated as a framework for humane animal testing as to try and regulate as much as possible the use of animals in scientific testing, as well as to push the scientific and medical arena into developing and adapting alternative models to human research, to decrease and minimize the use of animals and improve their welfare, which must balance out its costs and benefits to human knowledge, health and disease. Replacement reflects the need, whenever possible, for researchers to either replace the animal species with alternative methods; Reduction refers to the need for reducing as much as possible the number of animals upon which experiments are conducted on, without compromising the aim of the research; while Refinement is based on the idea that methodologies and procedures in animal testing should minimize as best as possible the distress, suffering, harm and pain inflicted and experienced by the animals (based on the idea of establishing a limit of objective pain perception that an animal model should be exposed to, and for the need to provide animals with sustainable and efficient husbandry and housing). The interaction of the three components of the principle of the Three Rs, has been an important step forward in the controlling and protection of animals used in laboratory experiments; nevertheless, the interaction of these three has been proven to be of a negative kind because of the conflict that can

arise when applying them to experimental decisions. This is because even if applied under EU and US legislation, there is no provision forcing researchers to use them collectively, and are thus normally used independently of one another. Using them independently raises a conflict between which of the three Rs to apply in a given experiment, and which should be of higher importance; when this occurs, there is no indicated provision to follow in case of conflict, making researchers decide on their own between which component is best suited to carry out the experiment in order to achieve the results wanted. When this conflict arises, for example, researchers tend to give higher importance to Replacement, as they prefer to improve experimental designs and findings rather than opting for Reduction as to decrease the number of animals used, or either decide to opt for Reduction as to reduce the quantity of animals used, yet exposing the fewer animals employed in the experiments under higher intensity of pain and distress. In fact tied to this is, another problem arises: even if under Refinement, legislations provide with the need of regulating the harm caused to animals, by placing a limit to the degree of pain an animal should be exposed to under experimental protocol, the perception of pain is hard to measure and most of the time researchers adopt inadequate measures of experimentation, exposing the animal to a pain that for the researcher might be considered acceptable and of worthy case in order to provide with the adequate findings they are looking to achieve. The problem is that not only there is a failure in giving enough weight to ethical concerns regarding animal testing in relation to the principle of the Three Rs, adopted by both EU and US legislations when these enter into conflict, but that even if required under law to share information between researchers, most failed experimentations are still rarely regulated and published by scientists or researchers. This is because, the legislations enacted specify the need to publish the findings obtained, but omit the publication of failed experimentations. Not only this places limitations on experiments and knowledge sharing between researchers, possibly pushing other researchers to conduct the same exact experiment without the knowledge of its failure, but also leads the public to lack access to the information regarding the ineffectiveness of animal testing whenever these do not provide with adequate, efficient or valid

findings. It is of key value and importance instead, for all kind of experimentation, whether successful or not, to be published and shared as to increase awareness, not only to spread medical knowledge between researchers as well as to increase human health, but also to provide with the reality of the ineffectiveness and waste of experimentation on animals and to push global efforts towards the application of alternative procedures which might result in being even more efficient than testing on animal models for human disease.

Introduction

In the scientific community, medical research has been an essential field for widening the range of knowledge regarding human health and diseases. Scientists and researchers, since Ancient Greece have focused on extrapolating information by conducting experimentation procedures on animals, used as models of human disease¹. The range of research fields covered by animal testing has increased tremendously since the 1950s, when new procedures were adopted as diseases and rare illnesses were starting to infect human populations. Up until today, animal experimentation has reached procedures of invasive kind, where animals are subjected to environment, behavior, and health manipulation, in most cases them being exposed to artificial diseases found in humans, in order to study the effects and reactions of such and to possibly provide and develop new drugs, treatments and cures. Animal experimentation can be said to have provided with essential medical information which has indeed furthered human knowledge by, for example, creating new vaccinations, cures and preventions to common diseases². Yet, the extended number of animals used and killed after and during testing, the invasiveness of the procedures, the inhumane treatments, the high degree of pain and suffering that the animals are exposed to, along with the deprivation of their natural environments and wildlife, has led to an increase in awareness and intense debates regarding the ethicality and morality of practicing invasive experimentations on animals, such as its necessity, acceptability, justification and the reliability and effectiveness of the research findings³. Science and medicine are indeed fields of worthy causes, nevertheless, through the technological developments achieved in the past decades, new alternatives have been proposed as to substitute the use of animals in research procedures, especially since many of the animal experiments conducted have indeed resembled to be wasteful and unreliable, where the benefits to humans are not proven to be efficient. The new non-invasive and humane alternatives go beyond the need for animal testing and animal cruelty, being also validated and promoted

¹ HOPES, Huntington's Outreach Project for Education, At Stanford, *The Ethics of Animal Experimentation*, 2010

² American Psychological Association, *Research Animals in Psychology: Animal Research Advances Animal and Human Welfare*, n.d.

³ Baumans V., *Use of Animals in Experimental Research: an Ethical Dilemma?*, Gene Therapy, 2004

by scientists to being more effective, reliable, precise, faster, less expensive and even safer than animal testing⁴. These models have shown that human well-being and health can still be obtained and promoted by adopting different sophisticated and nonviolent methods and approaches of investigation and prevention of disease, by also embracing ethical science.

1. The Context of the Debate

Animal experimentation in general refers to procedures that are performed on living non-human animals for research purposes in the fields of biology and diseases as to assess the potential and effectiveness of new medicinal products and human treatments, as well as examining human health along with environmental safety of products used by humans in their everyday lives. The problem relies in the fact that most of the experiments conducted subject the animals to high degrees of pain, suffering and distress, as well as the fact that they reduce the quality of their lives⁵. Most animals are required to be conscious and aware, them being treated inhumanely, with their environments and behaviors subjected to manipulation. Intense debates have roused as issues (such as its necessity, acceptability and justification have been raised in regards to research conducted on animals⁶. The ongoing debate on the matter about the ethics of animal experimentation has mainly focused on three potential, complex and different positions: “in favor”, “against” or in-between, known as “the middle-ground” position. A brief overview of the different views is essential in order to understand the ethics behind individual’s position on the matter.

1.1. The Case in Favor of Animal Experimentation

Those who claim to be in favor of animal experimentation claim that the use of animals has allowed and contributed to progress in medical and scientific

⁴ PETA, *Alternatives to Animal Testing*, n.d

⁵ HOPES, Huntington’s Outreach Project for Education, At Stanford, *The Ethics of Animal Experimentation*, 2010

⁶ NEAVS, New England Anti-Vivisection Society (n.d)

research and that without it the benefits would have not been obtained, as to understanding biological processes and biomedical discoveries, along with the founding of many preventive treatments and therapies like vaccines, antibiotics, insulin and organ transplantation⁷. They point out that experimentation on non-human animals should continue even though it subjects the subject to pain and suffering as the benefits to humanity are far more important and outweigh the costs towards the animals “sacrificed”, making it permissible and morally less significant to do so. For the defenders of animal testing, human beings have a higher moral status than non-human animals as belonging to a moral community means having more responsibility towards those who belong to it and share the same rights, than those who are considered to be part of a different one (even if theoretically the moral community of humans includes animals as well)⁸. The moment animals are seen as excluded from the moral community, those in favor view it as permissible to use them as tools for furthering research as they are believed to be inferior, lacking certain features and attributes in comparison to humans, such as for example intelligence, communication skills, and the ability to suffer and feel pain⁹.

1.2. The Case Against Animal Experimentation

The second position comprehends those against the use of animal experimentation, and who believe that it should immediately be stopped especially as new alternative ways for medical and scientific research can be used, as they have been provided by the technological progresses achieved and introduced throughout the 20th century. Some opponents question the real validity of the results obtained through the experimentations as they believe that the results obtained on an animal cannot really be transferable to humans, while other focus more on the ethical dilemmas of how animal experimentation brings horrific pain and suffering to the subjects, and the ethical question of whether it is right and acceptable for humans to subject animals to such procedures from

⁷ Nuffield Council on Bioethics, *The Ethics of Research Involving Animals*, 2005

⁸ Bernard E. Rollin, *Ethics of Medical Research with Animals*, The Hastings Center, 2012

⁹ Anderregg C., *A Critical Look at Animal Experimentation*, Medical Research Modernization Committee, 2006

which the animal will not benefit from¹⁰. They thus argue that an end to this type of research be placed, even though it might lead to consequences for the human, medical and scientific research progress, as they believe animals have a moral status (and the rights that come with that moral status) making it wrong to abuse or use them for human's own goals¹¹. They should be granted the equal level of treatment and respect as humans instead of supporting the claim that humans have a higher moral status ("*Speciesism*")¹².

1.3. The "Middle-Ground" Position

The third position instead, known as "middle-ground", is an in-between view between favoring and non-favoring animal experimentation. Proponents of this position believe that testing on animals is necessary in order to obtain scientific and medical progress, but because they feel uncomfortable with the damages, pain, distress, and suffering caused, they believe it is important to avoid animal experimentation whenever possible and ensure that experiments aren't replicated and that information is collected, reported and used appropriately, favoring as well alternative strategies whenever possible¹³. They perceive essential the need to give the best treatment possible to the animal subjected to the testing by reducing the pain and the suffering caused by the experimentation as well as improving the living conditions in the environments they are kept in. A hierarchy of moral standing reflects their view of using less complex organisms whenever possible over non-human mammals such as for example fruit flies, plants and bacteria, as those with a more complex organism are placed at the top of the moral hierarchy¹⁴.

¹⁰ Regan T., *Empty Cages: Animal Rights and Vivisection*, Cohen, Andrew and Wellman, Christopher eds. Blackwell Publishing, 2005

¹¹ HOPES, Huntington's Outreach Project for Education, At Stanford, *The Ethics of Animal Experimentation*, 2010

¹² Duignan B., *Speciesism*, Encyclopedia Britannica, 2013

¹³ Frey R.G., *Animals and Their Medical Use*, Cohen, Andrew and Wellman, Christopher eds. Blackwell Publishing, 2005

¹⁴ HOPES, Huntington's Outreach Project for Education, At Stanford, *The Ethics of Animal Experimentation*, 2010

Analyzing the three different positions, two main questions to the debate arise: firstly, “does the use of animals in the field of medical and scientific research provide with valid, relevant and useful results and knowledge (and that cannot be achieved otherwise)?” and secondly, “should it be morally acceptable and permissible for humans to cause extensive pain, suffering and death to animals as to obtain aims that mainly benefit the human community?”¹⁵. In order to consider and analyze the given questions one must first explore the different complex issues raised by testing on animals, such as the argumentation regarding the moral status of human and non-human animals along with the degree of pain, distress and suffering experienced by the subject of the experimentation.

1.4. The Three Different Positions of the Moral Status of Animal Experimentation

The debate, regarding animal experimentation, is often reduced to the question of the definition of the moral status, along with its moral importance, in relation to humans and non-human animals. By moral status and moral importance one refers to the different circumstances that make a being a member of a given community which include both moral agents and moral subjects (the former being those who possess the ability to behave morally and are accountable to moral criticism when morally failing, while with the latter it is meant a being whose features should be taken into account in relation to the behavior of the moral agent)¹⁶. In respect to the moral status different views and position can be identified: the first is known as the “*clear-line view*”, associated with *speciesism* (humans being superior to non-human animals), which places humans at the top the moral hierarchy as it is believed that they possess some morally vital property that instead all other non-human animals lack; this view is mainly supported by those who are in favor of animal experimentation¹⁷. Nevertheless, by assuming this position, such as considering humans as superior moral subjects compared

¹⁵ Gluck P.J., *Ethics and Behavior*, vol.1, 1991

¹⁶ DeGrazia D., *Taking Animals Seriously: Mental Life and Moral Status*, Cambridge University Press, 1996

¹⁷ Blosch M., *The History of Animal Welfare Law and the Future of Animal Rights*, The University of Western Ontario, 2012

to other species, this would still not explain and give enough valid explanation to why non-human animals should be sacrificed and abused of. In fact, even if human may be morally superior, humans should have the moral duty to protect, care and feel compassion towards the “lesser” creatures rather than using them in order to achieve means in order to allow them to live freely their lives without any interference by humans. This position can be tied to a “*competitive argument*” which underlines how species in order to survive compete with each other and for this reasons humans place its own specie at the top of the hierarchy¹⁸. This, though, still does not morally justify why humans should continue to use animals for their own benefits, even if the human species has survived by the domination towards other species. The reason of this is because humans developed the capacity to reflect upon their comportment through civilization and education, which linked together to other factors, has changed their natural behavior. Moving on, a second view can be tracked down: the “*moral sliding scale view*”, which sees the moral hierarchy to be correlated with a biological sliding scale of neurological complexity, comprising of humans at the top followed by primates and other mammals, and comprised with single-celled creatures and invertebrates at the bottom of the scale (this view is mainly supported by those supporting the middle-ground approach). Nevertheless, also this approach to a moral hierarchy faces the same challenges being posed by the clear-line view. Thirdly, there is the “*moral equality view*”, mainly supported by those against animal experimentation, which places no categorical distinction between species, giving them the same level of moral status and thus categorizes a classification of moral distinction to be insufficient as to explaining the justification of animal use¹⁹. For those under this position it is just a moral wrong to subject any animal to experimentation and unfair treatment, as it would be unacceptable if done to a human being²⁰. This view basically claims that if experimentation is carried out on animals and recognized as acceptable in order to achieve knowledge in research, then it would be acceptable and justifiable to do so also on humans, due to their equal moral status.

¹⁸ Darwin, C., *The Origins of the Species*, 1859

¹⁹ Animal Ethics Dilemma (AED), *The Animal Rights View*, n.d

²⁰ Regan T., *The Case for Animal Rights*, Oxford Blackwell ed., 1985

Nevertheless, neither three views answer the question of the permissibility and validity of using animals for scientific and medical purposes. What is essential, thus, is to understand what are the morally relevant features that characterize a human and a non-human animal in order to be classified as being a moral subject (and thus comprising of a moral status).

1.5. The Correlation Between Moral Status and Morally Relevant Features

Morally relevant features are important in understanding what characterizes and may qualify a subject, either human or non-human animal to be considered a moral one, in order to try and understand how they should be treated in general and not only towards the field of experimentation. The appropriate moral care of a being should not just depend on the species to which the subject belongs to but to the moral characteristics and features it possesses. The relevant features do provide with a sense of reason for moral apprehension, where animals having at least one or all features should be retained to be a moral subject and thus human interference with one of these features should require careful and precise justification when infringed upon it²¹. Five different features can be tracked and attributed to the moral status of a moral subject, where at least one or all of the features can be found to be applicable, even if differently, to different animals. It is essential to take the following features as relevant in order to understand how to make and take into account moral decisions in respect to the moral subject. These cognitive capacities are: sentience, high levels of cognitive capacities, the capability to flourish, sociability and the possession of a life²².

1.5.1. Sentience

The first cognitive feature has been mainly attributed with the famous utilitarian philosopher Jeremy Bentham, who described it as the capacity to feel

²¹ DeGrazia D., *Taking Animals Seriously: Mental Life and Moral Status*, Cambridge University Press, 1996

²² Nuffield Council on Bioethics, *The Ethics of Research Involving Animals*, 2005

pain and pleasure. In the past, animals were believed to lack the capacity to feel pain, but nowadays this view has changed as it has been proven that animals, especially those with a neurological complexity do have the capacity to feel pain²³. This nevertheless has been contested by many, especially by those conducting the experiments (scientific questions are preferred rather than the moral ones), as it is believed that humans have a different and more intense perception of pain than other species. As humans can also anticipate pain and suffering, and this not only could affect the individual subjected to it but also its social relations, for example by affecting the members of its family, some reach the conclusion that because human pain is more amplified than that of animals because of the consequences it brings, then it is more justifiable to conduct painful experiments on animals than on humans. The real problem relies in the fact that mostly all of the experiments do cause terrible pain and suffering to the animals involved in it, as well as the fact that they reduce the quality of their lives²⁴. If we consider these experiments to produce serious moral problems, then to cause animals to suffer should be considered a morally wrong action. What should be taken into account is not only considering the ethical responsibilities concerning causing animals pain, but also the horrid mental states that follow and accompany pain, such as for example states of discomfort, anxiety, distress or fear. If just the duration and intensity of the pain itself is cruel, then imagine the total negative experience that animals have to go through. Thus, the procedures have the potential to cause not only physical but also psychological suffering and distress to the animal, especially since most experiments require the animals to be awake and conscious, as it is scientifically believed that what animals do feel is similar to that of humans. But of course, pain and its perception varies significantly among the different animals within the different species that exist, nevertheless animal suffering must be given equal value and consideration to the suffering of most humans²⁵.

²³ Animal Ethics Dilemma (AED), *The Animal Rights View*, n.d

²⁴ Choose Cruelty Free, *Against Animal Testing: Animal Models are not Predictive*, n.d

²⁵ Nuffield Council on Bioethics, *The Ethics of Research Involving Animals*, 2005

1.5.2. High Levels of Cognitive Capacity

Apart from the capacity for animals to sense pain, many have also high cognitive capacities; these include the knowledge of the distinction between what is good and evil, the ability to possess a sense of self-consciousness, and the tenure of a certain type of rationality. The most important ones relate to the capacities of communication such as language and the capacity to perform them as planned, which have been normally attributed to signs of intelligence and exclusively traced to be attributes of the human species. Nevertheless, even if there are great controversies regarding the cognitive capacities animals might be entailed to have, many research made has combined not only biological but also philosophical expertise that has proved the ability of some animals, as for example great apes, dogs, birds and rodents, as to being able to develop these cognitive capacities associated to intelligence²⁶. These animals examined have showed to be able to learn complicated tasks, creating and the using of tools, but especially of possessing communication and engaging in social interactive behaviors. Therefore, compared to what was previously believed, it has now been proven that many animals do share many common relevant features, behaviors, abilities and dispositions to humans, which have been developed in order to survive in their natural habitat when encountered with the variety of situations faced in the course of their lives (a type of evolutionary development). Species may be different in relation to complexity, humans being the most complex one mainly in terms of behavior, nevertheless this difference is just a quantitative one and does not explain why a more complex specie should be considered to be more worthy and valuable and comprised of a superior ethical code of comportment²⁷.

1.5.3. The Capability to Flourish

The given moral relevant feature has been attributed mainly to the philosopher Aristotle, who came up with the concept of animals possessing a “*telos*”, a sense of good, otherwise seen as the ability of animals to have

²⁶ Nuffield Council on Bioethics, *The Ethics of Research Involving Animals*, 2005

²⁷ Joordens S., *The Ethics of Animal Research: The Dilemma and Alternative Approaches*, University of Toronto Scarborough, n.d

interests or specific needs, such as that of survival in their given environmental conditions and natural nature²⁸. By placing animals in experimental environments, such as for example cages, animals are not able to flourish whether exposed to painful or non-painful experiments, misery or even mortality. It is true that for humans it may be problematic to establish what type of life is best for an animal, as animals cannot communicate in the same exact language as humans, but the concept clearly highlights that preventing animals to flourish in the course of their natural lives and environments clearly violates their biological significant features. From here it can be said that the real question is not whether the subjected animal used for experimentation is placed in a natural or non-natural environment but whether these meet their needs and capacity to flourish. This concept should be considered relevant in understanding an animal's well being, apart from the freedoms it should have and the pain and suffering exposed to it, as other than physical pain there are other causes done to animals that can trigger greater damages. By taking into account that animals do fulfill their nature of living in different ways compared to humans, and that how an animal achieves these functions is what really comprises of its real nature, interfering with and preventing animals to achieve their *telos* will provoke a negative empirical state for the subjected animal. To determine whether it should be justified to inflict pain on animals, one must ask himself whether what is done to the individual animal itself is fair in relation to the natural course of life the animal should conduct. The ethical principal that animals should not be used, but especially have unnecessary pain inflicted upon them, has many times been justified on the ground that it benefits the public as a whole. Many veterinarians, scientists and researchers in fact believe in the ethical standard of the public but nevertheless consider the use of animals for their research as a privilege, where animals should be used with respect, gratitude, appreciation and with concern towards their essential needs and environments. Of course, science and medicine should be considered worthy cases, which deserve the attention of research and new discoveries, but this does not justify the manipulation of animal's behaviors and environments which prevents those subjected to fulfill the natural course of their lives, along with the unnecessary cruelty and extensive killing.

²⁸ The Hastings Center, *The Moral Status of Invasive Animal Research*, Report no.6, 2012

1.5.4. Sociability

Sociability has been identified as another important component of moral concern in regards of a moral subject. This tradition has mainly been influenced by the philosophy of the famous philosophers such as Karl Marx, Martin Heidegger and Ludwig Wittgenstein, who attributed the belonging and the basis of a community to be based on the creation of moral relations of duties and rights through for example the ability to communicate by the use of language or a type of dependence towards the members of that specific given community for either economic, social or other motives. If this moral component is not seen as equal to the previously described cognitive capabilities, then sociability itself should be considered essential in generating moral concern towards the animal subjected to experimentation. If this is the case, one must observe that animals have established linked relationships with humans' everyday lives and thus in some way do belong to the same community²⁹. There are different ways in which they interact with the human species as they bring pleasure to human lives as companions, when observed in their natural environments or even in zoos. In certain cultures, some animals have even been attributed some religious significance and treated in particular ways because of it. But animals are also used in order to provide food, transport, clothing, or even for sports (hunting or racing). This sociability link thus proves that animal even if belonging to a diverse specie to humans are sociably tied to the human moral and thus humans should have the duty to respect and engage in responsibilities towards them, just as it would be correct to do so towards another human being, member of the community³⁰.

1.5.5. Possession of a Life

Possession of a life might perhaps result in being, compared to the other moral relevant features previously analyzed, to be a more complex and challenging principle to evaluate, as it poses the question of the real value of life. Under this criterion, if it is believed that killing is a wrongful act, then this

²⁹ Nuffield Council on Bioethics, *The Ethics of Research Involving Animals*, 2005

³⁰ PETA, *Animal Testing is Bad Science*, n.d

consequently means that life itself is valuable . Some believe that especially because of the importance and value life has that, it is exactly because of this that experiments should be carried out on animals and not humans, as animals lack the sense of worthiness of life and are unaware of their existence, thus perceived to humans to matter less. Yet, even if animals might lack the worthiness of life, they have developed cognitive capabilities, self-consciousness and an awareness of sensory experiences throughout their natural evolution, which reflects their concern towards their moment-to-moment existence, for example by simply trying to survive. By doing so, animals do, in some way, attribute a certain type of value to life, even if it might be less complex than that of the human species; this is because each kind of animal develops their own mental nature appropriate to the physical nature they live in, in order to fulfill the life they are physically fitted to live³¹.

After assessing the question of moral status and the relevant features attributed to a moral subject, it is essential to further the understanding of the ethical implications of animal testing in regards to the nature of pain, distress, and suffering that animals experience with the procedure conducted on them used to further knowledge in the field of medical and scientific research. The following section will analyze the reality of animal pain, the evilness attributed to it, and the different principles used in order to explain pain in relation to animal experimentation.

1.6. The Reality of Animal Pain

Still today, as previously contested, amongst many scientists exists the notion that non-human subjects don't really possess the ability to perceive pain or merely that their perception of pain is of no practical significance since they are not able of expressing it and communicating it in the same language as humans. It is seen as uncertain to really understand what animals feel and if they feel pain or anything at all. Thus, many try to negate, neutralize and lessen the immorality and aggravations of the ethical issues of causing pain to animals, by

³¹ Donald J., *Natural Law and Natural Rights*, n.d

interrogating the reality of pain experienced by animals³². Despite their intrinsic inability to describe their pain, as instead humans do, it seems very unlikely that such determinations to approaching the precision of their pain will be possible compared to human pain. However, if the major ethical obligation humans have towards other species is to not inflict unnecessary or unjustifiable pain to them, then this presupposes that they can experience pain, especially if they are used for example as models for human pain research. If they couldn't, then these models would be completely pointless and useless. To discriminate against helpless animals just because they lack the same exact cognitive ability, such as language or moral judgment, compared to that humans possess, makes it is no more justifiable than, for example, discriminating against human beings that have severe mental illnesses or infants. The mentioning of individuals with mental illness and infants is made in order to explain that these two categories of moral subjects pertaining to the same community lack to complete the complex full criteria of relevant moral features which for some humans serve as to justify the use of animals in experimentation as animals may lack the same exact cognitive features as humans. If these two types of moral subjects lack for example, full autonomy or cognitive capabilities, such as language, it would still be considered immoral and unethical to use them for experimentation³³. If this ethics applies to infants and the mental ill, then it should also apply to animals.

1.6.1. *Pain: An Evil in Itself*

Pain is an evil not just as it is a harm or something bad, but merely because it is an evil in itself purely for the way it feels. In fact *pain* has been attributed to the meaning of “an unpleasant sensory and emotional experience associated with actual or potential tissue damage”³⁴. With pain comes *suffering* perceived as “a negative emotional state, which derives from adverse physical, physiological and psychological circumstances, in accordance with the cognitive capacity of the

³² Rollin BE., *Animal Pain, Scientific Ideology and the Reappropriation of Common Sense*, J Am Vet Med Assoc, 1987; Rollin BE, *Pain and Ideology in Human and Veterinary Medicine*, Semin Vet Med Surg, 1997

³³ HOPES, Huntington's Outreach Project for Education, At Stanford, *The Ethics of Animal Experimentation*, 2010

³⁴ International Association for the Study of Pain, *Pain Terminology*, 1994

specie and of the individual being, and its life experience”³⁵; and with pain and suffering comes *distress*: “severe pain, sorrow or anguish”³⁶. All kinds of suffering are undesirable, whether inflicted upon animal or humans. Generally, for humans, pain could result in being sometimes beneficial as it signals the presence of some problems in the field of disease or injury of the human body. Nevertheless, to experience pain is bad in and of itself, which is the reason why pain is usually avoided by both humans and animals. It is unnecessary to question the reasons behind the cruelty of pain, not only because it is bad in itself, but also because pain is an evil not just for the consequences it brings but mainly in its essential nature. Thus, giving and assessing magnitudes of suffering and pain to animals through experimentation is equally evil when it occurs, and not only due to the bad effects it produces but as an evil in itself³⁷. Likewise, if it is an evil to animals as it is to humans, then we should look at the ethical principle of attributing animals the presence of pain when experiments are inflicted upon them and by assuming this existence of pain inflicted, this deliberative infliction on animals is consequently a harm and an evil in itself and thus morally unjust and unethical. Animal suffering should thus be attributed the same equal consideration to that of most humans and in order to comprehend better why inflicting pain on animals should be considered unethical it is important to analyze the different principles that follow it.

1.6.2. The Equality Principle

The equality principle, also known as the “similarity principle”, is an ethical principal that follows from the statement that pain is an evil in itself. It holds that a fixed degree, cruelty or duration of pain is equally an evil for whoever experiences it, equally for humans as for animals. The problematic relies in the fact that humans have an intrinsic tendency to consider their own specie as the morally more relevant one, since it is the group of belonging. This form of

³⁵ Morton DB.; Hau J., *Welfare Assessment and Humane Endpoints, in Handbook of Laboratory Animal Science: Essential Principles and Practices*, 2nd Edition, Seattle, WA: CRC Press, 2002

³⁶ Pearsall J.; Trumble B. (editors), *Oxford English Reference Dictionary*, 2nd Edition, Oxford University Press, 2003

³⁷ Feinberg J., *Human Duties and Animal Rights*, Princeton University Press, 1980

predisposition is known as *speciesism*, where the human species has an inherent tendency to consider itself the more relevant specie merely due to the group of belonging and specific human traits. Nevertheless, this claim is not adequate in order to conclude that animals are less morally noteworthy. It should be irrelevant to determine the validity of inflicting pain upon an animal of a “lower” specie just because it is not of a “higher” one, even if the animal might feel less or different pain compared to a human being³⁸. Also, if animals are considered to be so similar to the human species so that testing on them can be carried out, then mainly since they are alike humans that they should have a moral obligation not to be tested upon. Either they are very dissimilar to humans that the results of animal tests cannot logically apply to humans, or they are so similar that it should be unethical to carry out further experimentations³⁹.

1.6.3. *The Justification Principle*

The Justification Principle is another principle implied when referring to the nature of pain to be a fundamental evil in itself, reflecting the fact that as pain is an evil, consequently whoever causes the pain to another human or non-human being that can experience the pain, must show and give accountability of the necessity and justification to cause that pain. As humans, punishment and conscientiously trying to inflict gratuitous suffering and pain upon other beings of the same species, is seen as a deep-rooted evil and consequently an ethical wrong to harm another being without justification. Thus, to use animals for personal and human benefit, by inflicting unjustifiable or unnecessary pain, is a wrongful act since pain is an evil, especially since it is challenging and hard to declare how strong a justification is for inflicting that pain in experiments⁴⁰. The justification used for animal testing is that pain is a necessary evil since sometimes causing great harm might do great good, since it provides more good on balance by producing great benefits to humanity, and thus this justification

³⁸ Singer P, *Animal Liberation*, HarperCollins Publications, New York, 1975; Ryder RD, *Animal Revolution: Changing Attitudes Towards Speciesism*, Berg Publishers, New York, 2000

³⁹ Tannenbaum J., *Ethics and Pain Research in Animals*, ILAR Journals, 1999

⁴⁰ Feinberg J., *Human Duties and Animal Rights*, Princeton University Press, 1980

should make cases for animal testing acceptable. Nevertheless, the level and amount of suffering of the number of animals used are way higher than the benefits obtained for humanity as a whole and thus do not provide a moral justification for doing so.

1.6.4. The Value Principle

If pain is an evil, then the more pain inflicted, the greater the evil is. Thus, if looking back at the previously explained justification principle, it is possible to claim and understand that the greater the pain caused in experiments to animals, the greater the justification of conducting the experiment should be. Nevertheless, the greater the pain the experimentation will cause, the greater must the value of the testing be, and if the value of an experimentation is what really justifies the level and kind of pain caused, ethical deliberation will take place⁴¹. But once again, animal use in research is not sufficiently valuable to justify and validate animal pain since the testing do not promise certain and practical benefits to humanity. The harms vs. the benefits are not balanced, since the damage and harm done to animals is something that is certain to happen if the experiments will be conducted, while the harms to humanity by not conducting the experimentations are unknown since one cannot be certain of the success and benefits that it will produce, they are unpredictable and inaccurate. Ethics dictates that each life has a value and shouldn't be overtaken by its potential value to humanity.

The ethical and moral issues that have arose in relation to animal experimentation can be said to have varied throughout time. From the start of the first testing procedures (vivisections) till the expanded range of fields of research testing introduced since the 1950's, the ethicality and morality of invasive experiments has drastically increased along with awareness⁴². In fact, procedures became too invasive and caused terrible pain and suffering to the animals, along with experiments proving the unreliability, and many times even inefficiency, of

⁴¹ BBC Ethics, *Animal Experimentation: A Difficult Issue*, 2014

⁴² Baumans V., *Use of Animals in Experimental Research: an Ethical Dilemma?*, Gene Therapy, 2004

the animal testing results achieved (even if passed animal safety testing). The next section will provide with an overview of the different forms and uses of animal experimentation and procedures, as to assess better understanding of the ethical and moral dilemmas raised.

2. The Main Forms of Animal Experimentation

Animals have commonly been used as models for human disease in the field of basic and biomedical research and as subjects for the testing and development of new drugs, vaccines along with other biological like antibiotics, in order to advance and improve human health ⁴³. Through the use of research, critical information was achieved furthering human knowledge of basic learning processes, like thirst, hunger or reproduction, along with essential information regarding the sensory processes: hearing, taste, vision, and pain perception. Cognitive studies conducted on animals have provided both an ecological and comparative perspective upon issues of the mind and intellect. While other experimentations, provided information on how both levels of cognition and sensory functions can depend on previous life experiences. Animal research has provided with knowledge on the modes of adaptation to changes, along with development, to all types of learning, and evolution, allowing identification and refinement of the main behavioral principles throughout which the creation of efficient methods for self-reliance and promoting learning was achieved ⁴⁴. It has been essential in understanding behaviors affected by environmental toxicants and psychoactive drugs, allowing a better comprehension of physical dependence and drug abuse. Through animal studies, treatment for drug dependence and disorders, like for example depression, anxiety and schizophrenia, have been created. Using them as models has required for scientists to create artificial conditions to the animal that may resemble the same medical disease or even injury of a human being. In fact, as originally conceived, historically the concept of using animals as tools for furthering knowledge, started as a response to the many infectious diseases which

⁴³ Humane Society International, *Animal Testing*, 2017

⁴⁴ American Psychological Association, *Research Animals in Psychology: Animal Research Advances Animal and Human Welfare*, n.d.

were present back then. This idea was based on another assumption: that if animals contracted the same disease to humans and then cured, that maybe the same cure could work for the patient ⁴⁵. In order to do so and for an animal to be considered as a valid biological model, it was originally believed that it required having the same symptoms, responses to treatment, and the same biological mechanism as a human, so to ensure the effectiveness and safety of new treatments. The origins of animal experimentation parallels to the development of science and medicine, which is rooted back to ancient Greece, along with Aristotle's and Hippocrates's theories ⁴⁶. A brief overview of the origins of invasive animal use is essential in order to understand and later analyze in depth the development of the new and different uses and approaches used to experiment on animal models.

2.1. From the Past to the Present: Early Forms of Animal Research

It can be stated that the ethical and scientific reasons behind animal research, in some respect, have varied little from the first experiments conducted in ancient Greece. Natural physicians and philosophers of ancient Greece believed that through the use of animals their knowledge regarding the complexity of the human and non-human organisms would increase. Understanding the malfunctioning of the human body along with the diseases and consequences of injuries, and the creation of treatments and cures was essential for human prosperity and resulted with the introduction of the first vivisection procedures. The use of animals in experimental research can also be traced back to Galen (130–201 AD), the Roman emperor Marcus Aurelius' physician, who conducted public physiological experiments and dissections of monkeys, pigs, elephants and dogs, providing for a basis for practices in the field of medicine also in the following centuries. He also engaged in developing theories on human psychology, anatomy, pharmacology and pathology, becoming very

⁴⁵ Andereg C., *A Critical Look at Animal Experimentation*, Medical Research Modernization Committee, 2006

⁴⁶ Baumans V., *Use of Animals in Experimental Research: an Ethical Dilemma?*, Gene Therapy, 2004

influential across Europe. After Galen, experimentations ceased till the start of the Renaissance, with the introduction of anatomical studies. In the 17th Century, with the development of animal studies in medical schools in Europe, experiments became increasingly invasive and complex, where anesthetics were absent in the vivisection procedures⁴⁷. Conducting invasive experiments was done without great moral issues This was mainly tied to the idea proposed by René Descartes (1596–1650), who believed that man and animals differed by the simple fact that humans possessed a mind capable of perceiving awareness and the capability of perceiving pain, while animals could not think. He later recognized that animals could perceive pain but because unable to think, they were unable to consciously perceive the experience of those feelings⁴⁸. With this view, came the famous quote by Jeremy Bentham (1789), who opposed, claiming that “the [real] question [was] not, can they reason? Nor, can they talk? But can they suffer”⁴⁹. With the discovery of anesthetics and with the publication of Darwin’s *Origin of Species*, in 1859, animals were starting to be seen as being very similar to humans. The similarities provided for an increase in the use of animal experimentation, which developed new disciplines of biomedical field such as cognitive behavioral research, behavioral psychology, research in the pharmacology industry, toxicity tests, and the creation of genetically modified animals⁵⁰. Nevertheless, with the increase of animal testing, in the early 1960s, also came an increase in the public awareness regarding the use of animals, which soon gave birth to wanting to prevent the extreme use of non-human animals, by creating new legislations under strong ethics morals against the invasiveness of the experimentations. Many opponents focused mainly on the ethical dilemma of whether humans had the right to use animals and cause them terrible pain for medical purposes, especially when history has proven that not all experimentations can be fully reliable, guaranteed to be successful, and where human benefits do not justify the

⁴⁷ French RD, *Antivivisection and Medical Science in Victorian Society*, Princeton University Press, 1975

⁴⁸ Baumans V., *Use of Animals in Experimental Research: an Ethical Dilemma?*, Gene Therapy, 2004

⁴⁹ Bentham J., *An Introduction to the Principles of Morals and Legislation*, Oxford: Clarendon Press, 1789

⁵⁰ NEAVS, *Animals in Science/Research*, 2017

harm caused to animals. In Britain, in 1876, arose the first legislation in the world in order to regulate animal research; this being a response to the increasing number of animals used in testing from 250 in 1881 (being the first year records were kept) to 95,000 in 1910. This new Act of 1876 allowed conducting experiments, nevertheless placed animal testing under regulation and authorization ⁵¹. While in the 20th century, ethical justification debates regarding animal research have been essential tools for further shaping legislation across Europe and America, giving birth to many organizations and institutions aimed at protecting animals in laboratories, wanting to take down the different forms of experimental research conducted on them, by also trying to spread awareness of the new alternatives to these experiments.

2.2. *Cognitive Behavioral Research*

Cognitive behavioral research, also known as behavioral psychological research, is a form of research aimed at understanding both the mind and behavior of human and nonhuman animal in order to advance the welfare of humans. Studying animal's behavior has been used in order to understand human's emotions; animals being used as models for the human behavior and mind, and for those conditions concerning mental disorders and diseases of neurological forms, such as mental illness, disorders associated with memory loss, addiction to drugs, and the human sensory and nervous system's functioning. Experimentations are conducted, to list a few, on the hearing, vision, thirst, hunger, reproduction, fetal development, perception of pain, stress, aggression, fear, maternal deprivation, drug abuse along with cigarette and alcohol dependence ⁵². For studying cases on the human nervous system animal models are used in order to study processes of recovery post-neutral damage, or for the finding of correlates of biological kind to anxiety, fear, or stress, along with other invasive procedures aimed at controlling animals' eating systems. In order to conduct such experiments, animals are placed under human

⁵¹ French RD, *Antivivisection and Medical Science in Victorian Society*, Princeton University Press, 1975

⁵² American Psychological Association, *Research Animals in Psychology: Animal Research Advances Animal and Human Welfare*, n.d.

manipulation to the disease or condition of human behavior or disorder. Animal's behaviors and environment are manipulated under invasive procedures done to the body and brain, even by controlling the genetic engineering of the animal model. Deprivation from water, food, sleep; social isolation, maternal deprivation, physical restraints, electric shocks, brain damages and implanted electrodes into the brain can be said to be some of the many condition animal face under this field of research. Also, in order to study accurately the behaviors and the mind, the animals are required to be aware and conscious, thus placed under high degree of pain and suffering. After the testing has been conducted, normally animals remain in distress due to their long recoveries, and many times never recover ⁵³.

2.2.1. Common Area of Behavioral Research: Drug Addiction and Abuse

Researchers, in order to study the effects given by drug addiction and abuse, conduct experimentations where animal models are subjected to becoming drug addicted, or alcohol and cigarette addicted by forcing them to ingest or inhale substances. One of the main aims of this type of conducted research was that, by creating artificial addictions on animals, humans would be able to decrease the drug and alcohol addiction problems of a country.

Nevertheless, these experiments have been proven inadequate, as animals not always responded to substances of addicting kind like humans did, causing no fundamental insight into the causes of self-destructing behavior or of drink addiction, and thus do not guarantee effective treatments for humans. The US Food and Drug Administration (FDA) reported that the failure for drugs to be efficient and reliable, has increased of 86 percent since 1985, despite all the refinements and advances achieved in this field of testing ⁵⁴. Also, half of the drugs that obtained approval have many times been withdrawn or relabeled because of grave or even deadly cases of adversity side effects on humans. An example of this, was the drug Vioxx, which in 2004 seemed to be human efficient and secure as proved by the positive findings on animal testing. Yet, after the

⁵³ NEAVS, *Animals in Cognitive Behavioral Research*, 2017

⁵⁴ PETA, *Animal Testing is Bad Science*, n.d

release the drug caused around 60,000 deaths just in the US. After the tragic event of the unreliability of side effect drugs, the FDA in 2007 reported that between 1998 and 2005 adverse side effect substances had doubled⁵⁵. All this underlined even more the fact that, even if animal models did appear to be reliable and adequate subjects for testing, they provided with uncertain data as there would always be some other factor or condition that would alter the research findings (because of the uncertainty variable). In fact, other factors that contaminate testing interpretation, seem to be always present. Animals continuously experience negative influences such as physical and mental stress. This condition alters findings by the fact that stress affects pulse, heart rate, muscular activity, blood pressure, and also levels of hormones in an organism. Studies have proven that animals in laboratories are indeed exposed to stress experiencing, which develops not only due to the procedures done on them, or the environment in which they are kept it, or the recovery they need to face after invasive procedures, but also from what is called "sympathy pain"; this form of stress refers to the ability of an animal to become more distressed when seeing another animal in pain and distress. Taking into consideration also the fact that animal models can be kept for decades in laboratories, and that the findings of the animal testing results are unreliable because of the many omissions and inaccuracies of the records, alternative approaches should be taken, not only to protect the high number of animals used in invalid experiments but also for the increasing human health.

2.2.2. Common Area of Behavioral Research: Maternal Deprivation

Maternal deprivation experiments are those conducted on “affection” research, where infants are separated from their mothers, either at birth or after a short time of cohabitation, kept in total isolation or with surrogate mothers made of cloth and wire, or by separating them from their mothers through a glass, in order for them to see but not touch them. Most of the maternal separation testing is carried out on monkeys and chimpanzees (as they share 98.8% of their DNA with humans)⁵⁶, in order to study and demonstrate the importance of maternal

⁵⁵ Topol EJ., *Failing the Public Health- Rofecoxib, Merck and the FDA*, New England Journal of Medicine, 2004

⁵⁶ American Museum of Natural History, *DNA Comparing Humans and Chimps*, New York, n.d

contact (because of this similarity, experimenting on these primates has raised very serious ethical disputes). Some infants were kept in isolation for their first 24 months of life, in what was labeled “wells of despair” as there were enclosed chambers in order to prevent light entering or interaction with the outside world. These experimentations exposed the animals to becoming totally destroyed, to the point of becoming non-functioning adults, whereas females artificially impregnated due to the destruction of the ability of social interaction, would give birth to infants whom they would not care for ⁵⁷. These studies have been categorized in three groups of research study: deprivation, affection and separation. The first category, as previously mentioned, included testing based on taking away the infant from the mother. The second category is said to represent the “nature of love” used to understand the attachment between the infant and mother. The third category of maternal deprivation, instead, included a collection of tests in order to understand the consequences of separating an infant from a mother (or another infant) after a bond of attachment was created between them. These experiments trace back to the early 1950s with the first deprivation studies based on affection, carried out by Harry Harlow who later, in the mid 1960s conducted the first maternal deprivation experiments, followed by in the early 1970s with separation experimentations which spread terror and subsequent psychopathology among the animal models used ⁵⁸.

2.2.3. Behavioral Research: Diseases That Affect Emotion and Behavior

In different research areas there is an interaction and overlapping for cognitive behavioral and biomedical research, due to the neurological component found in certain human disease processes affecting the cognitive, social, emotional and behavioral processes. Biomedical and behavioral researchers, engage together in animal testing under one protocol, for example for the testing of Parkinson’s or Alzheimer disease, in the attempt of creating an animal model of disease found in humans ⁵⁹. To do so the animal is

⁵⁷ Bowlby J., *Maternal Care and Mental Health*, Genova, WHO Monograph Series, Vol.2, 1952

⁵⁸ Cohen MJ, *A Critique of Maternal Deprivation Monkey Experiments*, The State University of New York Health Science Center, MRMC Report, 1996

⁵⁹ NEAVS, *Cognitive-Behavioral Research*, n.d

inflicted the disease process, either via spinal cord or brain damage, in order to mimic the human symptoms. Nevertheless, the tests have proven that even if the brain damage may mimic the symptoms of a human affected by Parkinson's, the test provides no information regarding the causes and the possible progression in the human body⁶⁰. To go forward and create a better model for human disease, researchers have developed new techniques by applying a genetic modification to the animal models as to detect patterns and pathways for new therapies towards these diseases.

2.3. Genetically Modified Animals: Gene Modification

Animal's genome modification has become a new process of research, which came to be throughout the ages. Originally, variations in the genetic composition occurred with the start of agriculture, where humans altered the process of reproduction (selective breeding) between animals based on the desired traits and also because, by altering the genome an animal would be able to increase, for example, milk production and feed conversion. Selective breeding was thus used as a tool for creating higher yielding and more productive farm animals, along with the increase in breeding animals having particular characteristics and features⁶¹. In recent times, researchers speeded the mutation process with the process of chemical mutagens and irradiation, increasing greatly the ability to study and manipulate genomes of animals in order to develop gene-detecting technologies, and understand fully the function and structure of the different human and non-human genes. Nevertheless, by injecting human disease or by gene modification, the animal models manipulated not only go through invasive, stressful and painful procedures, but are also likely to conduct lives full of health problems and high chances of increased lethality. Yet, the development of gene testing using engineering technology has been important for scientists to providing new tests for examining the toxicity and safety of products, chemicals, devices, and drugs, and for demonstrating how gene therapy products can correct defects of genetic type, or alleviate its symptoms, or even slow down the

⁶⁰ Emory University, Yerkes National Primate Research Center, *Alzheimers Disease- Yerkes Researchers Closer to Why Humans Develop it*, 2009

⁶¹ Nuffield Council on Bioethics, *The Ethics of Research Involving Animals*, 2005

progression of a disease. Gene modification, having been used as identifying the role of single genes throughout animal development, has led to the creation of genetically modified animals where the gene expression was increased or decreased. Nevertheless, implications of the testing conducted result in being difficult to determine and predict, as this form of experimentation has led either to no adverse effects or to severe development of abnormalities and disabilities towards the animal model⁶². Through the use gene technologies, researchers have advanced their field of research by focusing on animal cloning, a process based on generating an identical duplication of a cell, a gene or even an entire animal. This type of invasive procedure can be distinguished under two categories: the first being for reproduction reasons, while the second for therapeutic research. The former aims at reproducing an animal that is virtually identical in the genetic sequence from the predecessor from which it was duplicated and cloned, done as to ease the targeted genetic alteration of animals. The latter instead, refers to a type of cloning based on the use of techniques aimed at producing genetically identical embryonic stem cells to the donor of the nucleus. These, being in isolation from developing embryos, have the exclusive ability to evolve into various types of cells and duplicate indefinitely. Throughout this technique, therapeutic cloning, aimed at improving the scenarios for the development of cell substitution therapy in humans, has nevertheless proven that genetically foreign cells coming from another person or animal are rejected from an organism (unless the immune systems remains under control through potent pharmaceuticals that may need to be taken for numerous years)⁶³. It can be said, that both types of cloning and genetic modifications done on animal models has raised many concerns in public opinion. Research methods have resulted in being very inefficient and have required numerous repetitive attempts in order to achieve cloning or simple gene information transcription, along with carrying out negative implications for the animal. Such implications have shown to be, that by altering the gene sequence (by adding or removing DNA genes) various animals were

⁶² Lee T., *Gene Future*, New York, Plenum Pr, 1993

⁶³ Nuffield Council on Bioethics, *The Ethics of Research Involving Animals*, 2005

structurally and physically too large for a normal birth while others showed to display early signs of aging⁶⁴.

2.4. Research in the Pharmacology Industry

Animal testing has been a key element for all pharmaceutical companies in their process of development, discovery and production of new pharmaceutical products, as well as cosmetics and toxicology testing. Pharmaceutical industries test medicines and products on animals in order to ensure the safety of the product and the efficacy in treating a disease or condition, even if animal testing does not ensure a product's safety for consumers as animals have showed to react differently to some products compared to humans. Products, before being approved, released, and tested on consumers, are first tested on animals in order to assert the toxicology of the product and its possible side effects⁶⁵. The aim is thus to create new medicines and vaccinations, along with improving methods of toxicity testing and better diagnosis techniques. The development of this industry dates back to the late 19th century and beginning of the 20th century, when infectious diseases and injuries arose from mass migrations during WWI. During and after WWII, a systematic approach was made towards new medicines under animal research. Nevertheless, because the medicine's effects were measured in relation to the animal's physiological response, like blood pressure alteration, this method of screening, to discover useful effects of medicines, not only used huge number of animals but also showed to be inefficient and unreliable. With the expansion of pharmaceutical industries in the 1950s and 1960s, animal research grew, especially when in the 1980s new technological techniques and resources became easily accessible and integrated into the research process. It can be said that today's pharmaceutical research remains the main form of invasive testing conducted on animals because of the high number of animals used in testing for toxicology, like the LD50 test and drug/medicine reaction tests, and cosmetic testing such as testing eye irritancy, skin irritation, sensitization, corrosion and skin absorption of substances.

⁶⁴ Clark J.; Whitelaw B, *A future for Transgenic Livestock*, *Nat Rev Genet*, 2003

⁶⁵ Samuels G, *Medicines: Tried and Tested- In Animals?*, 2003

2.4.1. Toxicity Testing

The strictest tests in the pharmaceutical industry are preclinical toxicology tests on drugs and food. In fact, for example, in Europe these tests use one million animals every year; where in each chemical test approximately 50.000 animals. The tests performed can last less than a month to even years, just to test the general toxicity, mutagenicity, or carcinogenicity of a product, providing for essential information to assess risky and hazard potentials. Nevertheless, the high number of animals used has not provided accurate reflections of the effects of some toxins in humans, leading to false and unreliable results. Data from the severe tests conducted may possibly end up meeting classification and regulation labeling, but may be still of inadequate value for risky and hazard assessment, along with the fact that the doses of chemicals tested on animals are normally way higher doses than those prescribed or taken by humans. In fact, one famous common product safety test to measure the toxicity of doses of chemicals has been the LD50 (lethal dose 50 percent) based on forcing the animal subject to the testing (often rats, mice) to ingest the chemicals, through force feeding tubes, in order to determine the dose that would result in the death of fifty percent of the animals used. The forced ingestion would cause severe pain, discomfort and stress to the animal, especially when the standard test would require the use of 60-200 animals, all generally without pain relief nor anesthesia, as by doing so could alter the results of the testing. Apart from testing toxicity, the LD50 test aimed also at measuring the toxicity of powders and gases, the direct injection of substances into tissues and body cavities, and the effects of skin exposure such as internal poisoning and irritancy. Nevertheless, after strong debates and documentation of the failures of the LD50 test⁶⁶, this traditional test finally came to an end, but gave birth to new alternative testing methods for severe toxicity research, many of which still require the lethal use of animals ⁶⁷. Even if, with the end of the traditional toxicity tests, the number of animals used in the experimentations has decreased, the subjects used are still exposed to immense and severe pain, and many times face death (especially if

⁶⁶ Zbinden G, *Significance of the LD50 Test for the Toxicological Evaluation of Chemical Substances*, Archives of Toxicology, 1981

⁶⁷ Fano A., *Lethal Laws: Animal Testing, Human Health and Environmental Policy*, London, Zed Books, 1997

placed under chronic toxicity testing where animals at the end of the research are killed in order for the researcher to analyze signs of the body or organ system damaged by the chronic toxins).

2.4.2. *Cosmetic Testing*

Animal testing in cosmetics was introduced during the 1940s when serious injuries hit consumers exposed to unsafe and unreliable beauty products⁶⁸. Nowadays many pharmaceutical and cosmetic industries do not require for products to be exposed to animal testing as their formularies are based on reliable ingredients cataloged as safe. Yet, companies still prefer in testing cosmetics on animals as a response to legal protection against products that may harm a consumer whom petitions a lawsuit. The animal test, in this case, would be presented as evidence that they used due diligence in running safety testing⁶⁹. Animal models in the cosmetic industry however, have slightly decreased as a rising number of countries worldwide have passed laws that have banned the testing on cosmetics done on animal subjects, being a matter of great controversy. In some countries, like Belgium, Netherlands and the UK, cosmetic testing has been completely banned, while the European Union, in 2009, has passed a near-total ban on the cosmetics engaged with animal testing. Initially this European ban did not prevent cosmetic industries' products, which underwent animal safety testing, to be sold if the testing were to be conducted elsewhere from Europe, but in 2013 the testing outside Europe was also banned. As the main cosmetic companies in Europe were forced to end cosmetic testing on animals, in order to legally sell their products, new and alternative and more effective methods have been developed; however outside of Europe most of the cosmetic industries still tests the efficiency of the product on animals, exposing them to high degree of painful and stressful procedures. These cosmetic procedures mainly involve the testing of cosmetic eye irritancy and skin irritation. The most common method for testing the former, is the Draize test, which examines the

⁶⁸ Network Science, *The Process of Drug Development*, 2004

⁶⁹ Anderegg C., *A Critical Look at Animal Experimentation*, Medical Research Modernization Committee, 2006

irritancy of chemicals and products by releasing amounts of concentrated substances into the animal model's eye (frequently used are albino rabbits which possess sensitive eyes) and then evaluating the effects and reactions of the substance using a numerical subjective scoring, aimed at indicating the level of eye injury and damage, as for example the redness or the gradation of swelling. Many times these experiments cause also eye bleeding or even blindness to the animal, which is placed under immobilization (up to even 14 days) in body restraint stocks without being placed under anesthesia or pain reliefs⁷⁰. Still, the Draize test has provided many times with unreliable data as rabbits have showed, for example, to possess thinner and thus more easily damageable cornea than that of humans, making the prediction of human risks untrustworthy⁷¹. Due to the incomplete efficiency of the traditional Draize testing, alternatives such as the Isolated Chicken Eye Assay (ICE) and the Bovine Corneal Opacity and Permeability (BCOP) testing methods have been developed with the same aim: that of identifying products that may lead to permanent and severe eye damage. However, these two alternatives, even if less invasive than the first traditional test, still require the use and testing of animals. The same applies to tests conducted on skin irritation findings, along with allergic skin reactions, sensitization, corrosion and absorption tests. In fact, the test used to measure skin irritation through the harm, injury or even irreversible damages caused to the skin produced by a substance to an animal model, is typically conducted on rabbits by the traditional Draize skin testing method, by placing a substance on the animal's skin after being shaved and sometimes even by the removal of skin layers in order to trigger abrasions. These processes place the animal under tremendous pain, which is normally followed up by bleeding, scabs, and discoloration of the animal's skin. Alternatives to the invasive traditional Draize skin test, for testing the sensitiveness of skin, are commonly carried out using the Murine Local Lymph Node Assay (LLNA); however, such method still requires the use of animals for testing products and substances, and although the introduction of new forms of alternatives has decreased the number of animals used for this type of testing, animals are still killed at the end of every experimentation.

⁷⁰ NEAVS, *Product Development and Drug Testing: The Draize Test*, n.d

⁷¹ Sharp R., *The Draize Test- Motivations for Change*, Food and Chemical Toxicology, 1985

The prediction of corrosivity, toxicity and of other safety variables, along with the efficiency of save and new products for humans, has been achieved for centuries through the use of traditional invasive testing conducted on animals in order to test consumer products, new drugs, chemicals, and medical devices as to improve human health and knowledge. Yet today, scientists and researchers have validated and promoted new alternative techniques and procedures, resulting in being more effective and even safer than animal testing⁷². Through technological progress in this field of research, the challenge has been for countries to adapt and promote these new alternatives by creating some (even if very flexible) regulations and policies under legislation, as to not only ensure the findings of better data results that experiments might grant, but also as to protect the status quo of animals that undergo invasive procedures. The emphasis on the alternatives proposed and developed, have been placed mainly under European Union and United States' jurisdiction, which focus on concepts of replacement, reduction, and refinement in regards to the use of animals in experiments, while keeping and fostering the quality of scientific research and the safeguarding of human (and animal) health and environment⁷³.

3. The Way Forward: Meeting the Challenge

The real question lies in whether the different types of experimentations conducted on animals are useful for improving human health and knowledge, or just wasteful and unreliable. The problem lies also in the fact that, not only there is a failure in giving enough weight to ethical concerns regarding animal testing, but also that failed experimentations are rarely published by scientist and researchers, increasing unawareness of the public for the procedures conducted in laboratories and the access to information on the ineffectiveness of animal testing⁷⁴. Public unawareness in fact, has been one of the various key motivates for animal regulation, legislation and policies to be missing in a political, social and medical scenario. Nevertheless, with the rapid technological increase of fast information sharing, awareness has raises, leading some countries to establish

⁷² NEAVS, *In Testing*, n.d

⁷³ INFRAFRONTIER, *EU and National Regulations for Animal Experimentation*, 2013

⁷⁴ PETA, *Alternatives to Animal Testing*, n.d

some flexible regulatory measures, some based on the concept of the Three R's (Replacement, Reduction, and Refinement) ⁷⁵. Although some legislation has been passed, in most countries the lack of these, as to protect animals from invasive experiments that inflict pain and suffering on them, are still inexistent and underestimated; for animal testing being considered the only way forward to advancement. The belief of animals being the only tool for furthering knowledge, has been proven wrong by many scientists and researchers who provided with new and alternative non-violent and humane methods which would replace, or at least reduce, animal experimentation procedures, and possibly lead to the enforcement of animal protection under law, promising a brighter future for both animals and humans ⁷⁶.

3.1. Wasteful and Unreliable Experiments

As previously mentioned, a key question lies in whether the experimentations conducted on animals are useful or just wasteful and unreliable. Some believe and argue that even if it is wrong to unnecessarily abuse and inflict pain on animals, that the experimentation must continue as animal models provide important scientific resource. But the reality of animal experimentation is that most of the experiments conducted do not contribute in improving human health and diseases, as many medical treatments developed in animals rarely translate to human beings, and diseases which are artificially produced in animals in laboratories are never identical to those that take place naturally in humans. This is because many animals and humans are different biologically in many substantial ways, and thus the results obtained in animals will not yield and mirror the results that can be correctly applied to the human conditions. Symptoms and responses to potential laboratory treatment seen in other non-human subjects, for example, might result in being dissimilar to those of the human patients. Examples of this, according to the Director of the National Cancer Institute Dr. Richard Klausner, mice have been cured from cancer for decades, but the cures simply didn't work in humans. If instead we look at cases regarding HIV/AIDS, some 85 types of vaccines have been successful as a cure

⁷⁵ National Institute of Environmental Sciences (NIH), *Alternatives to Animal Testing*, n.d

⁷⁶ Humane Society International (HSI), *About Animal Testing*, n.d

in non-human primates, while for humans every one of these vaccines has failed to cure the disease. In one case, one of these effective vaccines on monkeys did not work in human clinical trials but instead it even made humans more susceptible in developing it ⁷⁷. Therefore, testing these types of vaccines on monkey was irrelevant to cure the disease on humans. A third example, relates to drug tests implemented on animals, where, as the U.S Food and Drug Administration declared, nine out of ten effective experimental drugs tested on animals did not accurately predict how they would behave in humans, as instead it did for the animals ⁷⁸. Also, some researchers from the Yale School of Medicine and various British universities, through the publication of a paper based on the examination of studies which had adopted an animal use approach and titled “Where is the Evidence That Animal Research Benefits Humans?”, managed to conclude not only that these experiments were wasteful and unreliable, but also that there was little evidence to prove and support the idea that all experimentation conducted on animals had benefitted humans and medical progress. In fact, many of the key advances in health have been instead attributed to human studies, as for example the finding of the correlation between heart disease and cholesterol or smoking and cancer, or even the creation and development of X-rays, or the AIDS virus’ isolation. What makes these experiments unreliable, depends on many factors, the main one being that animal models differ from human diseases. In fact, experimenters tend to examine the traits of the condition of the animal which bear a likeness with the characteristics of the human disease, commonly omitting the key physiological, anatomical and pathological divergence, misleading the real complexity of biological organisms. On top of that, the unnatural lab environments stress the animals, and consequently this stress influences negatively the entire organisms by either altering the blood and pulse pressure, the hormonal levels, the immunological activities and many more other factors ⁷⁹. The unreliability of animal testing’s finding, due to the various factors which do not ensure fully reliable results, has

⁷⁷ Simmons M, et al., *Cancer-Cure Story Raises New Questions*, *Los Angeles Times*, 1998.

⁷⁸ U.S. Food and Drug Administration, *FDA Issues Advice to Make Earliest Stages of Clinical Drug Development More Efficient*, FDA News Release, 2006.

⁷⁹ Pound P.; Ebrahim S.; Sandercock P. et al., *Where is the Evidence That Animal Research Benefits Humans?*, *Yale School of Medicine*, *British Medical Journal (BMJ)*, 2004

pushed scientists to adopting and addressing new alternatives to animal experimentation, not only to decrease the number of animals used, but also to increase the efficiency in research findings as to improve human health and medical knowledge.

3.2. Alternatives to the Problem of Animal Testing

Notwithstanding the rising evidence that it is time for a change, making the change possible within a scientific community, that has relied and was based for decades on non-human models as the “default method” for experimentation and research, requires perseverance and time as old habits die hard, but also because globally there is a scarcity of knowledge in non-animal techniques. The methods using animals continue not because it is the best science but because of archaic habits, practices, and resistance to change and thus progress. Familiarity and feeling comfortable with using animals push researchers not to feel in need of change, and perceive superior alternatives as high-risk innovation and technological change. Yet, through the numerous technological advances made in the field of medicine and research, new methods for testing have been created as alternatives to the classic methods. In fact, human epidemiological and clinical studies, human vitro studies on human cells and tissue methods, high-level human patient simulators, cadavers, computational models, are potentially alternative methods to research⁸⁰. These alternatives have proven to be more reliable, precise, faster and even less expensive, but especially they are humane alternatives to testing animals for the advancement of medicine. These models show that human well-being and health can still be obtained and promoted by adopting different sophisticated and nonviolent methods and approaches of investigation and prevention of disease, by also embracing ethical science.

3.2.1. Epidemiology Studies

Medical research has always aimed at identifying the main causes of disease in humans as to create and develop preventive and effective therapeutic

⁸⁰ The Hastings Center, *Ethics of Medical Research with Animals*, 2012

measures. In contrast to the artificial conditions created in animal models, human population studies such as epidemiology, have provided very useful, reliable, and humane findings in the field of human disease. This is because this field of research studies naturally occurring diseases and human health compared to the experimentally transmitted disease in animal models. In fact, the results obtained from data collection throughout the years in these longitudinal studies have granted health practitioners and researchers with the awareness of the causes, the understanding of cures and even with the preventions of different variety of human diseases⁸¹. This method of research has revealed to be an essential method as to identify risk factors for disease and the determination of optimal approaches to treatment in clinical practice, based on changes in lifestyle and with understanding the genetic functions and the possible environmental factors which contribute to illness. Epidemiological studies, for example, provided with the finding of the correlation and association between smoking and lung cancer, also being the first field of research which identified the AIDS disease (when in the late 1970s patients were affected by atypical infections). It also provided with the first real information and evidence regarding the causes, symptoms, and also possible preventions of heart disease, compared to what any other field of research had obtained previously and otherwise. In fact, the detection of the main threat components for coronary heart disease, such as high blood pressure, elevated cholesterol and smoking, that are considered essential factors for the creation of prevention methods, originate precisely from epidemiological studies⁸². Analogously, population studies have provided with evidence on cigarette smoking showing that the prolonged use from early adult life would triple the mortality rate, but if ceased at the age of 50 the dangers would be reduced by half, while if ceased at the age of 30 it would almost fully eradicate the danger and the future risk of mortality⁸³. These findings have been obtained through epidemiological studies based on extended over time observational and

⁸¹ Max Planck Institute for Biological Cybernetics, Department Physiology of Cognitive Processes, *Alternative Methods*, n.d

⁸² Unabel B et al., *Modelling the Decline in Coronary Heart Disease Deaths in England and Wales, 1981-2000: Comparing Contributions from Primary Prevention and Secondary Prevention*, British Medical Journal, 2005

⁸³ Doll R et al., *Mortality in Relation to Smoking: 50 Years' Observations on Male British Doctors*, British Medical Journal, 2005

retrospective studies, through observation and accurate data collection by researchers, without manipulating and inducing any disease in animal models.

3.2.2. *In Vitro Testing*

The *in vitro* testing is another alternative type of research that refers to procedural techniques performed in a regulated environment, conducted outside of a living organism, which has been proven by researchers and scientists to be superiorly efficient to animal testing. This alternative has been mainly taken into consideration by the Harvard's Wyss Institute which created engineered microchips called "organ-on-chips" which can be used to replicate the many functioning of human and non-human organs, like the intestine, kidneys, lungs, bone marrow, skin and blood-brain barrier; offering potential alternatives to the traditional use of animals testing in laboratories, substituting for example toxicology and cosmetic testing, as *in vitro* techniques provide with the identification of chemicals and substances of corrosive and irritant kind without testing them on animal models. These microchips are composed of a flexible and clear polymer containing microfluidic conduits combining and encompassing living human cells, which can mimic the whole physical microenvironment of living organs (even including, for example, breathing motions in lungs), along with allowing the controlling of the flowing of fluids and the viability of cells, providing a window into the inner working of living organs, along with real time observation that will provide researchers to study and analyze the complex interactions and correlations of the biochemical and physiological responses across the different organs tested. The development of these new human disease models aim at identifying new therapeutics targets and clinical biomarkers, along with facilitating the development of new vaccinations, drugs, pharmaceuticals, and the potential of finding and creating new medicines to cure human diseases without approaching traditional animal experimentation⁸⁴.

⁸⁴ Harvard's Wyss Institute, *Harvard's Wyss Institute Creates Living Human Gut-On-a-Chip*, 2012

3.2.3. Computer (*In Silico*) Models

The rapid technological increase in the field of computer processing has permitted the emergence of computer modeling *in silico* experimentations, based on research performed through the use of computer simulations using models which reflect closely the real world by simulating human biology and the development of evolving diseases. A vast part of *in silico* computer technology was initially developed by pharmaceutical industries for the discovery of adverse drugs as an alternative to adopting animal models to test the efficiency of drugs and substances. Here, drugs are drawn up to have physico-chemical features that augment distribution, absorption, excretion and also metabolism through the variety of types of *in silico* methods that have been created to illustrate and foresee toxicology results in both the environment and humans⁸⁵. In fact, the United States Environmental Protection Agency (US EPA) defines *in silico* toxicology as the “*integration of modern computing and information technology with molecular biology to improve agency prioritization of data requirements and risk assessment of chemicals*” (US EPA, 2003). Also, research studies have shown the accuracy of these models to predict the effect of new adverse drugs in humans, and the possibility of replacing the use of animal models in research of exploratory kind, along with substituting many standard testing on drugs. This is because the methods for *in silico* computer modeling comprise of a variety of computer techniques able to predict high-tech estimations of likely adverse and risky substances, through the Quantitative Structure-Activity Relationships method (QSAR), databases, data analysis tool, machine learning, network analysis tools, data mining, homology models, pharmacophores, and also other molecular approach methods. The way the *in silico* method works is that it reproduced computational models of illnesses and treatment, along with collecting and managing millions of data points of human research, where clinical human trials are carried virtually on computer model programs, able to mimic functions of anatomical kind, such as heart rate. Researchers, apart from assuring the effectiveness of this method as an alternative to animal usage, have reported that *in silico* computer and mathematical methods provide relevant advantages: tests conducted and data collected are of better quality and based on higher precise and accurate

⁸⁵ Stuttgart, *Improving the Welfare of Animals: Researchers Develop Computer-Aided Models to Replace Animal Testing*, Insilico Biotechnology, 2013

techniques and simulations because of the highly sophisticated technological models used, able to grant higher productivity in research finding in shorter time periods, where data information sharing is easily accessible to researchers and the whole scientific community enabling rapid identification of dangerous drugs; not to mention that this technique would reduce the number of animals used for testing in laboratories⁸⁶.

3.2.4. Autopsies and Biopsies

Human autopsies refers to examinations, carried out after death, of the organs and tissues of the human body in order to detect the causes of mortality, the prevalence of pathological conditions, the health state before death and provide with understanding whether any medical diagnosis and cure given to the subject before death were appropriate⁸⁷. In fact, this type of research can be said to having been accountable for the discovery of thousands of illnesses like viral hepatitis, aplastic anemia, heart disease, diabetes, appendicitis, fetal alcohol syndrome and even Alzheimer's disease⁸⁸. This is because, even if the practicality of autopsies is normally restricted to the lethal stage of the disease, biopsies can deliver essential knowledge regarding other disease stages. Biopsies can also be conducted on living patients, by using for example endoscopic and needle diagnostic procedures which allow the safe extrapolation of living tissues from the patient in order to study the tissue and conduct experiments on it to study disease and treatments. An example of this relates to endoscopic biopsies which have revealed the derivation of colon cancers from tumors of benign kind called adenomas. In contrast to this, experimentations conducted on animal models to detect such cancers failed to demonstrate such correlation as animals seem to lack this adenoma-leading-to-cancer sequence⁸⁹.

⁸⁶ Max Planck Institute for Biological Cybernetics, Department Physiology of Cognitive Processes, *Alternative Methods: Computer Simulations*, n.d

⁸⁷ Kapis MB, *Human Autopsies in Biomedical Research*, Ann Arbor, MI: Lewis Publishers, 1993

⁸⁸ Hill RB; Anderson RE, *The Autopsy: Medical Practice and Public Policy*, Boston, Butterworth, 1988

⁸⁹ Ahnen DJ., *Are Animal Models of Colon Cancer Relevant to Human Disease?*, Digestive Disease & Sciences, 1985

3.2.5. *Research with Human Volunteers: Clinical Studies*

Human clinical studies have been a key type of primary research, based on prudently, reliable and trusted architected and controlled studies on human volunteers, which have yield fundamental findings without using animal models nor harming human organisms and lives. These studies are of no harmful kind (cruelty-free) to patients in human medicine, as well as to animals in veterinary medicine, which has allowed researchers to investigate human and environmental conditions, diseases and possible treatments, without manipulating artifacts in laboratories, which might distort the findings from the conditions of artificial kind⁹⁰. These clinical studies are based on procedures conducted using devices such as PET, MRI, CAT, and SPECT scans, which allow the observation and evaluation of diseases found in human patients, which until today have strongly contributed in advancing medical modern knowledge, revolutionizing clinical examination. Because these procedures are non-invasive to humans, no ethical issues should be raised in these studies as individuals are free to participate or be excluded from them, as these are performed under the highest ethical standards⁹¹. In fact, most of the individual volunteers who decided to participate in such clinical case studies have chosen to be exposed to the non-invasive procedures as they being affected by either ordinary or terminal disease and thus willing to volunteer in order to help researchers find new drugs, cures and treatments, or simply be part of studies based on data collection regarding their disease. Also, the number of patients exposed to volunteering has shown that this field of research does not lack a shortage of volunteers, and that along with epidemiological studies, these two methods of research may in fact resemble in being the best two alternatives to animal testing for the efficient and reliable results they provide.

These technological advances in the field of medicine and research have shown to provide and grant alternatives for understanding and treating diseases, along with finding and testing new effective and safe drugs and pharmaceuticals in the field of human health, diseases, and general medical knowledge. With the

⁹⁰ NEAVS, *In Research: Clinical Studies*, n.d

⁹¹ Heimlich HJ, *Advantages and Safety of Clinical Research*, in Cohen M, Natelson N (eds.), *Facing The Challenge*, 1990

rise of awareness, and the extreme abuses inflicted upon animals used in wasteful and unreliable experimentations, changes in medical and research attitude are slowly taking place. Reducing the number of animal used and enforcing controls on test conducted throughout new legislations, regulations and policies proposed and passed mainly by the European Union and the United States, highlight the start of a new push towards global efforts as to encourage the progressive transition away from having to use animals in laboratories, especially when non-invasive, effective and reliable alternatives exist.

3.3. EU and US Legislation on Animal Experimentation

The welfare and protection of animals has been a topic enclosed by a variety of both European Union (EU) and United States (US) regulations under legislation, including the protection not only of animals used in experimentations for scientific reasons but also regarding the wildlife, zoo and farm animals, and animal transportation. In this section the focus will orient towards the legislation aimed at protecting animals in research testing. Under EU legislation, animal protection dates back to 1986, when the first legislation was created, covering animal use in the scientific field⁹². In fact, in 1986, a first Directive (86/609/ECC) was adopted by the European Council of Ministers, aimed at improving the regulation on the use of animals in laboratories by setting standards of minimum use and housing, along with the aim of enforcing the supervision and training of researchers who conduct experimentations, establishing that alternative methods should be adopted whenever possible in order to reduce the number of animals used and as to encourage validation and the development of these alternative methods. Nevertheless, since the adoption of the first legislation Directive, scientific and technological progress has been achieved, providing with new and sustainable methods for experimentation, pushing the European Commission to revise this first Directive, in order to make and indorse enhancements in the protection and welfare of animals. The revision led, in 2010, to the update and replacement of the Directive with a more solid one: Directive 2010/63/EU, which came into effect in 2013, with the aim of strengthening even more the legislation and improving animal's welfare by anchoring a new principle based on the

⁹² Infrafrontier, *EU and National Regulations for Animal Experimentation*, n.d

concept of the Three Rs (Replacement, Reduction and Refinement)⁹³. The same was carried out in US legislation, where animal's use was (and till today still holds) controlled by the Animal Welfare Act and by the Health Research Expansion Act. The most important of the two is the Animal Welfare Act, which dates back to 1966, when it was issued, and later amended in 1976 and 1980. Both of the amendments require the application of a minimum set of standards, aimed at minimizing the distress and pain inflicted on animals, requiring, just like the EU Directive, for researchers to take in consideration alternative methods to research before decided to conduct experimentation on animal models. The two Acts also establish the requirement for research facility for experiments to be approved and monitored by an Institutional Animal Care and Use Committee, as to evaluate the possibility of distress or pain prior to any testing conducted, in order to avoid unnecessary usage of animals (this also being based on the principle of the Three Rs)⁹⁴. Animal research, thus, whether used for producing or developing new medicines, or for drug, substance and chemical testing, or for the studying of environmental effects, or even physiological research (just to list a few), must be carried out in compliance with EU and US legislations, where animals' welfare costs must balance out the benefits to human knowledge, health and disease. In order to ensure the best cost/benefit analysis, both legislations consider essential factors such as the procedure's design and their relevance to human health and the advancement to knowledge they provide, the correct utilization of species along with the quantity of animals used, and the appropriate husbandry provided for the animals in laboratories, but especially, as previously mentioned, the need to adhere to the principle of the Three Rs.

3.3.1. The Principle of the Three Rs

Replacement, Reduction and Refinement are the components of the principle of the Three Rs, which was a concept developed in 1959 by William

⁹³ Official journal of The European Union, *Directive 2010/63/EU of The European Parliament and of The Council of 22 September 2010 on the Protection of Animals Used for Scientific Purposes*, 2010

⁹⁴ Metzger MM, *Knowledge of the Animal Welfare Act and Animal Welfare Regulations Influences Attitudes toward Animal Research*, J Am Assoc Lab Anim Sci., 2015

Russell and Rex Burch⁹⁵, two British academic members of the Universities Federation of Animal Welfare (UFAW) – an association based on the welfare and wellbeing of animals. This concept was later integrated in EU and US legislation (also in the British one), as a framework for humane animal testing as to try and regulate as much as possible the use of animals in scientific testing, as well as to push the scientific and medical arena into developing and adapting alternative models to human research to decrease and minimize the use of animals and improve their welfare. Replacement in fact reflects the need, whenever possible, for researchers to either replace the animal species tested with a specie comprised of a less complex neurological system (partial replacement) or even better for them to adopt alternative cruelty-free methodologies and testing strategies, eliminating completely the use of animal model in the procedures (absolute replacement). This absolute replacement is the major challenge today in the research field, and has been carried out by substituting animal use with, for example, as previously mentioned, with new *in vitro* techniques, *in silico* computer modelling, or even through clinical trials on human volunteers. Reduction instead refers to the need for reducing as much as possible the number of animals upon which experiments are conducted on, without compromising the aim of the research. This is either done by obtaining comparable levels of findings from smaller number of animals, or by obtaining greater information using the same animal model, improving the design of the experiment and analytical statistics, resources and data sharing. The last concept instead is Refinement, based on the idea that methodologies and procedures in animal testing should minimize as best as possible the distress, suffering, harm and pain inflicted and experienced by the animals. This aspect is not only tied to the idea of establishing a limit of objective pain perception that an animal model should be exposed to, but refers also to the need to apply refinement also to the environment (husbandry and housing) the animals are kept in⁹⁶. Accommodation,

⁹⁵ Russell WMS, Burch RL. *The Principles of Humane Experimental Technique*. Methuen: London, 1959, Reprinted by UFAW, 1992: 8 Hamilton Close, South Mimms, Potters Bar, Herts EN6 3QD England.

⁹⁶ Committee on Animal Research and Ethics (CARE), *Guidelines for Ethical Conduct in the Care and Use of Nonhuman Animals in Research: Care and Housing of Laboratory Animals*, 2012

care and breeding are factors that should not be underestimated by researchers, as they directly affect the health and well-being of the animals (inadequate environments cause physiological changes, stress and irregular behaviors), but also affect and compromise the validity of research findings⁹⁷.

3.3.2. *The Problem with the Three Rs' Principle*

The interaction of the three components of the principle of the Three Rs, has been a step forward in the controlling and protection of animals used in laboratory experiments in the field of research; nevertheless, the interaction of these three (Replacement, Reduction, and Refinement) has been proven to be of a negative kind because of the conflict that can arise when applying them to experimental decisions. The main problem is, in fact, that they can enter into conflict between each other even if taken in consideration and placed under EU and US legislation, as the Directives under it, even if providing for the need of applying these three concepts in experimental procedures, does not mention nor force researchers to use them collectively, thus them being used most of the time independently from one another. Using them independently raises a conflict between which of the three R concepts to apply in a given experiment and which should be of higher importance; when this occurs, there is no indicated provision to follow in case of conflict, making researchers decide on their own between which component is best suited to carry out the experiment in order to achieve the results wanted⁹⁸. In fact, most of the time, when the conflict arises, researchers tend to opt for the Replacement component, giving it major importance compared to, for example Reduction, as most researchers tend to prefer the improvement of experimental design and findings rather than reducing the number of animals used. Whenever instead researchers opted for the Reduction component as to reduce the quantity of animal models, it has been showed that by doing so the animal used are exposed to higher intensity of pain and distress. Another problem with the principle of the Three Rs, is that even if it provides for regulating the environment of animals and the harm caused to them, by placing a limit to the

⁹⁷ Zurlo J.; Rudacille D.; Goldberg AM, *The Three R's: The Way Forward*, 1996

⁹⁸ Ibrahim DM., *Reduce, Refine, Replace: The Failure of the Three R's and the Future of Animal Experimentation*, University of Chicago Legal Forum, Vol. 2006: Iss.1

degree of pain an animal should experience under experimental protocol, the perception of pain is hard to measure and most of the time researchers adopt inadequate measures of experimentation, exposing the animal to a pain that for the researcher might be considered acceptable and of worthy case in order to provide with the adequate findings they are looking to achieve. For example, the EU Directive provides for researchers, whenever possible, to provide, under experimentation procedures, for animals to be exposed to anesthesia or other types of pain relief as to decrease the suffering of animals. Nevertheless, the Directive provides but does not oblige researchers to adopt such measures, granting them the possibility of deciding by themselves whether to expose the animal to pain reliefs or conduct the testing without the use of any tranquillizer. As adapting such protocol could alter and confound the findings of the research, experimenters most of the time prefer to expose the animal to the procedure without using such, and under law it can do so by legally withholding pain relief⁹⁹.

3.3.3. Lack of Research Transparency and Public Awareness

The problem is that not only there is a failure in giving enough weight to ethical concerns regarding animal testing in relation to the principle of the Three Rs, adopted by both EU and US legislations when these enter into conflict, but that even if required under law to share information between researchers, most failed experimentations are still rarely regulated and published by scientists or researchers. This is because, the legislations enacted specify the need to publish the findings obtained, but omits the publication of failed experimentations¹⁰⁰. Not only this places limitations on experiments and knowledge sharing between researchers, possibly pushing other researchers to conduct the same exact experiment without the knowledge of its failure, but also leads the public to lack access to the information regarding the ineffectiveness of animal testing whenever these do not provide with adequate, efficient or valid findings. It is of key value and importance instead, for all kind of experimentation, whether successful or not, to be published and shared as to increase awareness not only

⁹⁹ NAVS, *Failure of Laws and Regulations to Protect Animals*, n.d

¹⁰⁰ NAVS, *Lack of Transparency in Reporting*, n.d

to spread medical knowledge between researchers as well as to increase human health, but also to provide with the reality of the ineffectiveness and waste of experimentation on animals, to push global efforts towards the application of alternative procedures which might result in being even more efficient than testing on animal models for human disease. Apart from the European Union and the United States (including the United Kingdom), this problem mainly rises in other countries, where the problem arises especially because only a small proportion of countries worldwide collect and then publish the data concerning the results on animal use, or the exact number of animals that are used in laboratories each year. Regulations, on the importance of complete transparency about this type of animal use, are essential and should therefore be included in the official figures of each country performing it. Countries should also not lack of adequate regulatory measures so as to protect the animals from the experiments that inflict pain and suffering on them, and which will lead to no further knowledge and discoveries, especially when alternative measures are available nowadays. Change and awareness are essential; animals should not be viewed as tools for research and education but instead be protected by laws. Governments, educational institutions, researchers and the community as a whole, should be committed in bringing this radical change as to reduce and subsequently eliminate as much as possible the use of animals in these invasive fields of research thanks to the alternatives that technological progress has provided in the last decades.

Conclusion: The Future of Animal Experimentation

The ethical and moral status of invasive animal research is what sparked the need for changing and moving towards a vision far from the classic need for traditional methodologies to be carried out in scientific laboratories using animals as models for human disease. From the first testing procedures till the expanded range of fields of research testing introduced since the 1950's, the ethicality and morality of invasive experiments has drastically increased and along with it arose the need for alternative methods to substitute such procedures, which most of the time proved to be unreliable, inefficient and wasteful¹⁰¹. With the promotion of

¹⁰¹ HOPES, Huntington's Outreach Project for Education, At Stanford, *The Ethics of Animal*

valid and humane alternative techniques, possible thanks to the technological progress achieved in the last decades, the challenge to move away from traditional testing is now possible, providing with not only better findings of data results, as to still allow the increase in scientific knowledge, human health and disease, but also as to protect and improve the status quo of the animals that undergo invasive procedures. Moving towards a far better future for animals in experimentation is slowly taking place, and regulations are starting to arise in order to slowly give enough weight to ethical concerns regarding animal usage as to prove the scientific community and the public, that has relied and was based for decades on non-human models as the default method for experimentation, that there are indeed other alternatives than that of using animals as tools for furthering human knowledge. Notwithstanding the rising evidence that it is time for a change, making the change possible within a scientific community, requires perseverance and time, as old habits die hard; animal research in fact, continues not because it is the best science but because of archaic habits, practices, and resistance to change and thus progress. Nevertheless, alternatives have proven to be more reliable, precise, faster, less expensive, but especially they are humane alternatives to testing animals for the advancement of medicine. These models show that human well-being and health can still be obtained and promoted by adopting different sophisticated and nonviolent methods and approaches of investigation and prevention of disease, by also embracing ethical science¹⁰². Alternatives are proof that change is possible, highlighting the need for a push to be taken towards collective global efforts as to encourage and allow the progressive transition away from having to use animals in the field of invasive experimental research. To make a step forward in order to meet the challenge also means that failing to treat animals appropriately is a moral failing as animals do not lack a soul, and should be treated under principles of beneficence and non-maleficence, especially in the field of medical research, as they are part of our community. It is the essence of morality to guard and protect these fundamental values; our moral responsibility towards them by ensuring that pain and unnecessary, unreliable and unethical experiments are not conducted on them. Animals may lack rationality, and thus lack to respond to moral claims and

Experimentation, 2010

¹⁰² The Hastings Center, *Ethics of Medical Research with Animals*, 2012

reason, but should be protected from invasive use. Rationality should be ignored because we all belong to the same kind.

Bibliography

- Ahnen DJ., *Are Animal Models of Colon Cancer Relevant to Human Disease?*, Digestive Disease & Sciences, 1985
- American Museum of Natural History, *DNA Comparing Humans and Chimps*, New York, n.d, <http://www.amnh.org>
- American Psychological Association, *Research Animals in Psychology: Animal Research Advances Animal and Human Welfare*, n.d, <http://apa.org>
- Anderegg C., *A Critical Look at Animal Experimentation*, Medical Research Modernization Committee, 2006
- Animal Ethics Dilemma (AED), *The Animal Rights View*, n.d, <http://www.aedilemma.net>
- Baumans V., *Use of Animals in Experimental Research: an Ethical Dilemma?*, Gene Therapy, 2004
- BBC Ethics, *Animal Experimentation: A Difficult Issue*, 2014, <http://www.bbc.co.uk>
- Bentham J., *An Introduction to the Principles of Morals and Legislation*, Oxford: Clarendon Press, 1789
- Bernard E.Rollin, *Ethics of Medical Research with Animals*, The Hastings Center, 2012
- Blosh M., *The History of Animal Welfare Law and the Future of Animal Rights*, The University of Western Ontario, 2012
- Bowlby J., *Maternal Care and Mental Health*, Genova, WHO Monograph Series, Vol.2, 1952
- Choose Cruelty Free, *Against Animal Testing: Animal Models are not Predictive*, n.d, <http://www.choosecrueltyfree.org.au>

- Clark J.; Whitelaw B, *A future for Transgenic Livestock*, *Nat Rev Genet*, 2003
- Cohen MJ, *A Critique of Maternal Deprivation Monkey Experiments*, The State University of New York Health Science Center, MRMC Report, 1996
- Committee on Animal Research and Ethics (CARE), *Guidelines for Ethical Conduct in the Care and Use of Nonhuman Animals in Research: Care and Housing of Laboratory Animals*, 2012
- Darwin, C., *The Origins of the Species*, 1859
- DeGrazia D., *Taking Animals Seriously: Mental Life and Moral Status*, Cambridge University Press, 1996
- Doll R et al., *Mortality in Relation to Smoking: 50 Years' Observations on Male British Doctors*, *British Medical Journal*, 2005
- Donald J., *Natural Law and Natural Rights*, n.d
- Duignan B., *Speciesism*, *Encyclopedia Britannica*, 2013
- Emory University, Yerkes National Primate Research Center, *Alzheimer's Disease- Yerkes Researchers Closer to Why Humans Develop it*, 2009
- Ibrahim DM., *Reduce, Refine, Replace: The Failure of the Three R's and the Future of Animal Experimentation*, *University of Chicago Legal Forum*, Vol. 2006: Iss.1
- Fano A., *Lethal Laws: Animal Testing, Human Health and Environmental Policy*, London, Zed Books, 1997
- Feinberg J., *Human Duties and Animal Rights*, Princeton University Press, 1980
- French RD, *Antivivisection and Medical Science in Victorian Society*, Princeton University Press, 1975

Frey R.G., *Animals and Their Medical Use*, Cohen, Andrew and Wellman, Christopher eds. Blackwell Publishing, 2005

Gluck P.J., *Ethics and Behavior*, vol.1, 1991

Harvard's Wyss Institute, *Harvard's Wyss Institute Creates Living Human Gut-On-a-Chip*, 2012

Heimlich HJ, *Advantages and Safety of Clinical Research*, in Cohen M, Natelson N (eds.), *Facing The Challenge*, 1990

Hill RB; Anderson RE, *The Autopsy: Medical Practice and Public Policy*, Boston, Butterworth, 1988

HOPES, Huntington's Outreach Project for Education, At Stanford, *The Ethics of Animal Experimentation*, 2010

Humane Society International (HSI), About Animal Testing, n.d, <http://www.hsi.org>

Humane Society International, *Animal Testing*, 2017, <http://www.hsi.org>

INFRAFRONTIER, *EU and National Regulations for Animal Experimentation*, 2013, <https://www.infrafrontier.eu>

International Association for the Study of Pain, *Pain Terminology*, 1994, <http://www.iasp-pain.org>

Joordens S., *The Ethics of Animal Research: The Dilemma and Alternative Approaches*, University of Toronto Scarborough, n.d

Kapis MB, *Human Autopsies in Biomedical Research*, Ann Arbor, MI: Lewis Publishers, 1993

Lee T., *Gene Future*, New York, Plenum Pr, 1993

Max Planck Institute for Biological Cybernetics, Department Physiology of Cognitive Processes, *Alternative Methods: Computer Simulations*, n.d

Metzger MM, *Knowledge of the Animal Welfare Act and Animal Welfare Regulations Influences Attitudes toward Animal Research*, J Am Assoc. Lab Anim. Sci., 2015

Morton DB.; Hau J., *Welfare Assessment and Humane Endpoints*, in *Handbook of Laboratory Animal Science: Essential Principles and Practices*, 2nd Edition, Seattle, WA: CRC Press, 2002

National Institute of Environmental Sciences (NIH), *Alternatives to Animal Testing*, n.d, <http://nih.gov>

NAVS, *Failure of Laws and Regulations to Protect Animals*, n.d, <http://www.navs.org>

NAVS, *Lack of Transparency in Reporting*, n.d, <http://www.navs.org>

NEAVS, *Animals in Cognitive Behavioral Research*, 2017, <http://www.navs.org>

NEAVS, *In Research: Clinical Studies*, n.d, <http://www.navs.org>

NEAVS, *Product Development and Drug Testing: The Draize Test*, n.d, <http://www.navs.org>

Network Science, *The Process of Drug Development*, 2004

Nuffield Council on Bioethics, *The Ethics of Research Involving Animals*, 2005

Official journal of The European Union, *Directive 2010/63/EU of The European Parliament and of The Council of 22 September 2010 on the Protection of Animals Used for Scientific Purposes*, 2010

Pearsall J.; Trumble B. (editors), Oxford English Reference Dictionary, 2nd Edition, Oxford University Press, 2003

PETA, *Alternatives to Animal Testing*, n.d, <http://www.peta.org>

PETA, *Animal Testing is Bad Science*, n.d, <http://www.peta.org>

Pound P.; Ebrahim S.; Sandercock P. et al., *Where is the Evidence That Animal Research Benefits Humans?*, Yale School of Medicine, British Medical Journal (BMJ), 2004

Regan T., *Empty Cages: Animal Rights and Vivisection*, Cohen, Andrew and Wellman, Christopher eds. Blackwell Publishing, 2005

Regan T., *The Case for Animal Rights*, Oxford Blackwell ed., 1985

Rollin BE., *Animal Pain, Scientific Ideology and the Reappropriation of Common Sense*, J Am Vet Med Assoc., 1987;

Rollin BE, *Pain and Ideology in Human and Veterinary Medicine*, Semin. Vet Med Surg., 1997

Russell WMS, Burch RL. *The Principles of Humane Experimental Technique*. Methuen: London, 1959, Reprinted by UFAW, 1992: 8 Hamilton Close, South Mimms, Potters Bar, Herts EN6 3QD England.

Samuels G, *Medicines: Tried and Tested- In Animals?*, 2003

Abstract (in Italian)

Lo stato etico e morale della ricerca invasiva condotta sugli animali è ciò che ha scatenato la necessità di un cambiamento e la necessità di spingersi oltre la classica visione, basata sul bisogno di eseguire nei laboratori scientifici metodologie tradizionali, e sull'utilizzo degli animali come modelli per simulare malattie umane, nel campo della ricerca classica e quella biomedica, ma anche usati come soggetti per testare e sviluppare nuovi farmaci, vaccini, cure e prevenzione per malattie comuni, con lo scopo di migliorare le conoscenze mediche e della salute umana. Fin dalla nascita della sperimentazione animale, che risale all'Antica Grecia, la ricerca medica è stata per certo un campo essenziale per l'amplificazione della gamma di conoscenze in materia di salute umana e malattie, includendo anche conoscenze di apprendimento basico come la sete, la fame e la riproduzione, provvedendo anche informazioni utili sui processi sensoriali come l'udito, il gusto, la visione e la percezione del dolore. Si può dire che, a partire dal 1950, la gamma dei settori di ricerca basati sulla sperimentazione animale, sono aumentati drasticamente in conseguenza dell'aumento di malattie e infezioni che hanno colpito le popolazioni, portando quindi alla necessità di nuove cure e trattamenti risolutivi. Studi cognitivi condotti su animali hanno fornito anche una prospettiva sia ecologica che comparativa, su temi riguardanti la mente e l'intelletto umano; mentre altre sperimentazioni hanno fornito informazioni su come entrambi i livelli delle funzioni cognitive e sensoriali dipendano da precedenti esperienze di vita. La ricerca animale ha infatti fornito le conoscenze sulle modalità di adattamento ai cambiamenti, sull'evoluzione e lo sviluppo di tutti i diversi tipi di apprendimento, permettendo l'identificazione dei più importanti principi comportamentali, tramite il quale è stata ottenuta la creazione di metodi efficaci per promuovere l'apprendimento. La ricerca è stata fondamentale anche riguardo la comprensione di quei comportamenti influenzati da agenti tossici ambientali e da farmaci psicoattivi, permettendo una migliore consapevolezza circa le dipendenze fisiche dell'uomo e l'abuso di droghe e alcol. Tramite gli studi condotti sugli animali, sono stati anche sviluppati trattamenti per la tossicodipendenza

e i disturbi come la depressione, l'ansia e la schizofrenia. Nonostante l'importanza della scienza e della medicina, che sono campi di cause meritevoli, la sperimentazione animale ha fatto affidamento in esperimenti sottoponendo gli animali ad elevati gradi di dolore, sofferenza ed angoscia, oltre a causare una riduzione di qualità di vita degli animali stessi. Questo perché, fino ad oggi la sperimentazione animale ha raggiunto procedure di tipo estremamente invasivo, dove gli animali sono sottoposti a manipolazioni ambientali, comportamentali e salutari, nella maggior parte dei casi esponendoli a malattie artificiali riscontrate nell'uomo. Il numero esteso di animali usati e uccisi dopo e durante le procedure di sperimentazione, l'invasività delle procedure, i trattamenti inumani, l'elevato grado di dolore e sofferenza a cui gli animali vengono sottoposti, senza considerare la privazione dai loro ambienti naturali, ha portato ad un aumento della consapevolezza tra tutte le persone e ad intensi dibattiti riguardanti l'eticità e la moralità circa la pratica di questi metodi così invasivi. Discussioni riguardanti la necessità, l'accettabilità, la giustificazione, l'affidabilità e l'efficacia dei risultati della ricerca in questione. In realtà il dibattito in corso sulla questione circa l'etica della sperimentazione animale, si è concentrata principalmente su tre possibili, complesse e diverse posizioni: chi a favore, chi contro, o chi in una posizione intermedia. Queste si concentrano principalmente sul dilemma etico, basato sulla questione riguardante il diritto che l'uomo dovrebbe esercitare sull'usufruire dell'utilizzo di animali nel campo della ricerca, o sul diritto di infliggere loro terribili dolori, soprattutto quando in passato la sperimentazione ha dimostrato che non tutte le procedure sono pienamente affidabili, non garantendo il pieno successo, e dove i benefici per l'uomo non giustificano i danni causati. Analizzando le tre diverse posizioni, sorgono nel dibattito due questioni principali, in primo luogo, se davvero l'utilizzo degli animali nel campo della ricerca medica e scientifica, fornisca realmente validi, pertinenti e utili risultati e conoscenze, i quali non potrebbero essere raggiunti altrimenti per allargare le conoscenze umane. In secondo luogo sorge la questione morale: è moralmente accettabile e lecito per gli esseri umani causare dolore, sofferenza e anche la morte ad animali allo scopo di ottenere obiettivi e benefici soprattutto per la comunità umana. Al fine di

analizzare e considerare i punti indicati è necessario dapprima esplorare le diverse questioni sollevate dalla sperimentazione sugli animali, come ad esempio l'argomentazione per quanto riguarda lo status morale, il grado di dolore, l'angoscia e la sofferenza vissuta dal soggetto sotto ricerca. La discussione è spesso ridotta alla questione del fornire un'adeguata definizione sullo status e al valore morale, in relazione agli esseri umani o animali. Per quanto riguarda lo status morale diversi punti di vista e posizioni possono essere così identificati: la prima posizione pone l'essere umano in cima alla gerarchia morale, in quanto esso ritiene di possedere diverse proprietà moralmente vitali che invece tutti gli altri animali non hanno (principalmente supportato da coloro che sono a favore della sperimentazione animale). La seconda si basa ugualmente sul concetto della superiorità morale dell'uomo, ma pone la necessità ed il dovere morale essenziale da parte dell'uomo nei confronti delle altre specie, di doverle proteggere, curare e provare compassione verso queste creature "minori", piuttosto che utilizzarle come strumenti al fine di promuovere la conoscenza umana. In terzo luogo vi è la posizione sostenuta principalmente da coloro che sono contro la sperimentazione animale, che non pone nessuna distinzione categorica tra le specie, dando loro infatti lo stesso livello di status morale e quindi non ritenendo sufficiente questa categorizzazione per spiegare e giustificazione l'uso degli animali. Viene visto di conseguenza moralmente sbagliato ed inaccettabile sottoporre animali alla sperimentazione e al trattamento sleale, come lo sarebbe se condotto sul genere umano. Questo punto di vista sostiene principalmente che, se la sperimentazione venisse effettuata su animali e riconosciuta accettabile per conseguire nuove conoscenze nel campo della ricerca, allora sarebbe anche accettabile e giustificabile farlo sull'essere umano, avendo essi lo stesso status morale. Nessuno dei tre diversi punti di vista tuttavia risponde alla domanda sull' ammissibilità e la validità nell'utilizzo degli animali per scopi scientifici e medici. E' essenziale quindi capire quali sono le caratteristiche moralmente rilevanti che caratterizzano un essere umano e animale per poter essere classificato come un soggetto morale (e quindi con status morale), e per poter capire quale adeguato trattamento si dovrebbe utilizzare sugli animali testati in campo della ricerca e non. Questo perché l'appropriata attenzione morale non

dovrebbe basarsi soltanto in relazione alla specie a cui il soggetto appartiene, ma anche sulle rilevanti caratteristiche morali e comportamentali che esso possiede, in quanto forniscono un senso di gravità morale, perché gli animali con una o tutte queste caratteristiche dovrebbero essere considerati soggetti morali, e dove l'interferenza da parte dell'essere umano richiede un'attenta e precisa giustificazione quando questi vengono violati. È quindi indispensabile adottare le seguenti caratteristiche come fattori rilevanti, al fine di capire come fare e come prendere in considerazione le decisioni morali in relazione al soggetto morale: sensibilità, alti livelli di capacità cognitive, capacità di prosperare, la socialità e il possesso della vita. Dopo aver valutato la questione circa lo status morale e le sue caratteristiche è essenziale chiarire la comprensione delle implicazioni etiche sulla sperimentazione animale per quanto riguarda la natura e la realtà del dolore, dell'angoscia, e della sofferenza che gli animali subiscono tramite le procedure invasive a cui sono sottoposti per la ricerca. Tuttavia si può dire che le questioni etiche e morali sorte in relazione alla sperimentazione animale, sono stati strumenti essenziali e determinanti non solo per la creazione di normative (principalmente in Europa e negli Stati Uniti) ma dando vita anche a molte organizzazioni e istituzioni volte a proteggere gli animali nei laboratori, con lo scopo di sconfiggere e abbattere la vasta gamma di procedure di ricerca sperimentale condotte sugli animali. Queste forme di sperimentazione rientrano in un'ampia gamma di categorie di ricerca. Una di queste è la ricerca cognitiva-comportamentale, che si basa sul comprendere sia la mente e che il comportamento umano (e non), al fine di migliorare il benessere dell'uomo. Sotto questa categoria di ricerca gli esperimenti vengono effettuati, per citarne alcuni, sull'udito, la visione, la sete, la fame, la riproduzione, lo sviluppo fetale, la percezione del dolore, lo stress, l'aggressività, la paura, la deprivazione materna, l'abuso e la dipendenza a fumo, alcol e droghe. Un altro ramo di tipo invasivo della ricerca scientifica, si basa sulla modificazione dei geni animali e sugli animali geneticamente modificati (clonazione), con lo scopo da parte del ricercatore di accelerare il processo di mutazione cellulare animale attraverso processi di mutageni chimici e di irraggiamento, permettendo così di studiare e manipolare genomi di animali, allo scopo di sviluppare

tecnologie di rilevamento genetico e comprendere appieno la funzione e la struttura dei diversi geni umani e non. Iniettando virus di malattie umane od eseguendo modificazioni genetiche, tuttavia, i modelli animali manipolati non solo vengono sottoposti a procedure molto invasive, stressanti e dolorose, ma sono anche soggetti a condurre una vita piena di problemi di salute e con un'alta percentuale di mortalità. La sperimentazione animale è un elemento chiave anche in campo farmaceutico per il processo di scoperta, sviluppo e per favorire la produzione di nuovi prodotti del settore, basandosi su test cosmetici e tossicologici. Le industrie farmaceutiche infatti, testano farmaci e prodotti su animali, al fine di garantire la sicurezza del prodotto e l'efficacia nel trattare malattie e condizioni, pur se la sperimentazione animale ha dimostrato di non garantire sempre la sicurezza del prodotto per il consumatore, in quanto gli animali spesso reagiscono in modo diverso al farmaco utilizzato a confronto dell'essere umano. I prodotti stessi pertanto, prima di essere approvati, rilasciati, vengono infatti prima testati sugli animali al fine di affermare o meno la tossicità del prodotto in questione ed esaminando attentamente i suoi possibili effetti collaterali. Questi esperimenti, tuttavia, sono stati dimostrati inadeguati, perché gli animali non sempre hanno risposto alle sostanze come hanno fatto invece gli esseri umani e non portando quindi alcun miglioramento sia in materia scientifica che medica, sia nell'ambito delle malattie che delle cure, e quindi non garantendo trattamenti altamente efficaci per gli esseri umani. Tutto questo sottolinea ancor di più il fatto che, anche se i modelli animali sembrano essere soggetti affidabili ed adeguati per la sperimentazione, essi forniscono dati relativamente certi dovuto a fattori o condizioni che in qualche modo modificano e alterano le conclusioni della ricerca. È fondamentale, proprio per questo, capire se i diversi tipi di sperimentazioni siano davvero utili per migliorare la salute umana e la conoscenza medica e scientifica, o se le procedure invasive in alternativa siano solo uno spreco in quanto inaffidabili. Alcuni sostengono che anche se fosse sbagliato abusare ed infliggere dolore agli animali, la sperimentazione debba continuare, perché i modelli animali nonostante tutto, forniscono importanti risorse scientifiche. La realtà della sperimentazione animale è che la maggior parte degli esperimenti condotti non contribuiscono a migliorare la salute e le malattie umane,

e questo perché svariati trattamenti medici necessariamente sviluppati negli animali di rado sono stati tradotti in modo equivalente negli esseri umani, e anche le malattie che vengono riprodotte artificialmente negli animali di laboratorio, non sono mai identiche a quelle che avvengono naturalmente nel corpo umano. Ciò è dovuto al fatto che gli esseri animali e umani si differenziano biologicamente tra loro in molti modi, e che quindi i risultati ottenuti negli animali non produrranno e rispecchieranno mai del tutto validi risultati, applicati di conseguenza correttamente alle condizioni umane. L'inaffidabilità dei risultati di questa sperimentazione, dovuta ai diversi fattori che non garantiscono in pieno la certezza della validità dei risultati, ha spinto scienziati e ricercatori ad adottare e indirizzare la comunità scientifica verso nuove alternative circa l'uso dell'animale, non solo per diminuirne il numero usato, ma anche per favorire l'aumento dell'efficacia dei risultati ottenuti con la ricerca, per migliorare quindi lo stato della salute umana, le conoscenze mediche ed il benessere degli animali. Tramite il rapido progresso tecnologico ottenuto nel campo della medicina e della ricerca nuovi metodi sono stati creati in alternativa ai classici metodi di approccio. Questi si basano su studi epidemiologici e clinici, sull'utilizzo di tecniche *in vitro* su cellule e tessuti umani, su simulatori umani di alta tecnologia, cadaveri e modelli *in silico* computazionali e matematici. Queste alternative sono ritenute essere più affidabili, precise, veloci e meno costose ma soprattutto sono considerate tecniche opzionali alternative alla sperimentazione condotta sugli animali per il miglioramento della medicina. Questi nuovi modelli dimostrano che sia il benessere che la salute dell'uomo possono essere ugualmente raggiunti e sviluppati utilizzando metodi diversi, più sofisticati e meno violenti, i quali tengono in conto il valore dell'etica scientifica e morale. Con l'introduzione di questi nuovi metodi, cambiamenti nel comportamento medico e di ricerca stanno pian piano prendendo forma. La riduzione del numero degli animali usati e il maggiore controllo sui test di ricerca derivano non solo dalle nuove tecniche alternative proposte dai ricercatori, ma anche dalle nuove leggi approvate principalmente dall'Unione Europea e dagli Stati Uniti, evidenziando l'inizio di uno sprint verso una collaborazione che favorirà, a livello globale, la transizione graduale dall'utilizzo di animali nei laboratori

all'uso di alternative non invasive, più efficaci ed affidabili. Le legislazioni adottate mirano a rafforzare e migliorare il benessere dell'animale, ancorate al famoso concetto delle "Tre R" (Rimpiazzare, Ridurre e Rifinire), integrate come contesto per favorire tecniche umane e alternative alla sperimentazione indotta su animali da laboratorio. Utile e necessario per cercare di regolare il più possibile l'uso di animali in test scientifici, per spingere lo scenario scientifico e medico a sviluppare e adottare questi nuovi e alternativi modelli di ricerca, per diminuire e minimizzare l'uso di animali e migliorandone il loro benessere, il tutto per bilanciare costi e benefici della conoscenza medica e sulla salute. Il "Rimpiazzamento" riflette la necessità per i ricercatori, qualora possibile, di sostituire la specie animale con metodi alternativi; il concetto di "Riduzione" fa riferimento, invece, al bisogno di ridurre il più possibile il numero di animali usati, senza compromettere lo scopo della ricerca scientifica. Il terzo concetto, "Rifinire", si basa sull'idea che le metodologie e le procedure nel campo della sperimentazione animale, debbano e dovrebbero ridurre al minimo, nel miglior modo possibile, il disagio, la sofferenza, il male, ed il dolore inflitto e vissuto dagli animali (questo concetto si basa sull'idea di stabilire un obiettivo limite di percezione al dolore a cui gli animali possano essere esposti, e al bisogno di fornire all'animale, soggetto di ricerca, con ambienti, alloggi e allevamento di tipo sostenibile ed efficace). L'interazione delle tre componenti del principio delle "tre R", è stato un importante passo avanti nel controllo e nella protezione degli animali utilizzati negli esperimenti di laboratorio; tuttavia, l'interazione di questi tre concetti ha dimostrato di essere di tipo negativo a causa del conflitto che può sorgere quando vengono applicati a decisioni sperimentali. Questo perché, anche se applicati sotto le legislazioni Europee e Americane, non c'è alcun regolamento che obblighi i ricercatori ad usare le "tre R" collettivamente, infatti vengono usate nella maggior parte dei casi in modo indipendente fra loro. Applicare i concetti in modo indipendente solleva la questione su quale favorire delle tre R e a cui dare maggiore importanza; non vi è infatti alcuna disposizione indicata da seguire sul come muoversi in caso di scelta, permettendo quindi ai ricercatori di decidere autonomamente quale componente sia il più adatto per condurre l'esperimento con lo scopo di

ottenere i risultati voluti. Molte volte i ricercatori tendono a dare maggiore importanza al concetto di "Rimpiazzamento", in quanto preferiscono il miglioramento del design sperimentale piuttosto che l'optare per la "Riduzione", che diminuirebbe il numero di animali utilizzati. In cambio, molte volte, coloro che hanno preferito optare per il concetto di "Riduzione", per permettere di diminuire il numero di animali usati, li hanno conseguenzialmente esposti a maggiori intensità di dolore e angoscia durante gli esperimenti. Infatti, legato a questo, è correlato un altro problema: anche se sotto il concetto di "Rifinire" le legislazioni adottate prevedono il bisogno di regolare la quantità e il limite di dolore (applicato su modelli animali sotto protocollo sperimentale), la percezione del dolore è difficile da misurare, e nella maggior parte dei casi i ricercatori adottano metodi inadeguati per calibrare il livello di dolore stesso, esponendo pertanto l'animale ad un'elevata intensità e ad alti gradi di dolore, considerati però accettabili per il ricercatore e che, vengono ritenuti tollerabili al fine di fornire i risultati previsti, molto più importanti. Il problema quindi sorge, non solo dovuto al fallimento nel valutare e stabilire un adeguato e sufficiente peso alla percezione del dolore, ma principalmente nel dare il giusto peso all'etica morale e scientifica riguardante la sperimentazione animale in relazione al principio delle "Tre R", quando esse entrano in conflitto tra loro. Pur se richiesto dalle leggi Europee e Americane di adottare la condivisione di informazioni e dei risultati delle ricerche, la maggior parte degli esperimenti con esito negativo, non vengono condivisi da scienziati e ricercatori, questo perché le legislazioni emanate specificano la necessità di pubblicare gli esiti dei risultati ottenuti, ma omettono la necessità di pubblicare le sperimentazioni fallite. Questo pone dei limiti alla sperimentazione e alla condivisione delle conoscenze tra i ricercatori stessi, spingendo altri ricercatori ignari a condurre quegli stessi esperimenti (e con l'utilizzo delle stesse procedure, e ottenendo gli stessi esiti fallimentari), ma porta anche la comunità in sé per sé a non avere accesso alle informazioni essenziali riguardanti l'inefficacia di molte sperimentazioni e quanto queste non forniscono risultati adeguati, efficienti e validi. E' di essenziale valore, invece, che ogni tipo di ricerca, che sia che di successo o meno, venga pubblicata e condivisa per aumentare la consapevolezza

e la trasparenza di informazioni tra le persone comuni, per diffondere le conoscenze mediche tra ricercatori, ottimizzare lo stato della salute umana, fornire un senso reale alla vera inefficacia e spreco della vasta gamma di tipologie e procedure sperimentali sugli animali, rafforzare il benessere degli stessi, ma soprattutto per diffondere e spingere la comunità globale a fare quel grande passo in avanti verso un futuro scientifico migliore, basato su metodi alternativi di grande e profondo valore umano, etico e morale, che ugualmente daranno la possibilità a tutto il mondo di migliorare le proprie conoscenze in campo medico e scientifico, sostituendo parzialmente o del tutto l'uso degli animali presi a modello per essere testati allo scopo di favorire la ricerca.