Human-animal chimeras through induced pluripotent stem cells
Beyond the current legal framework

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"In ancient civilizations, chimeras were associated with God,(…) and our ancestors thought "the chimeric form can guard humans." In a sense, that's what our team hopes human-animal hybrids will one day do. "

- Jun Wu in *National Geographic* (2017)

Table of contents

1. Introduction chapter

In January 2017, a team of international researchers from the Salk Institute for Biological Studies reported their creation of the first successful human-animal chimera using induced pluripotent stem cells (hereafter: IPSs). This ground-breaking research, creating animal embryos injected with human stem cells, opened doors in various scientific fields. A human-animal chimera is a hybrid creature, consisting of cells of two different species. The name finds its origin in Greek mythology, belonging to an animal which was a combination of a lion, a goat and a snake, an on top of this was able to spew fire. The Salk Institute team created a slightly less imaginative chimera, namely a human-pig chimera, using the new technology of IPSs. IPSs are a type of artificially created stem cells originating from mature somatic cells, which are reprogrammed 'back' into pluripotent stem cells. Pluripotent stem cells are cells that have the ability to differentiate into one of any of the three germ layers. This feature makes them of enormous importance since pluripotent cells thus have the ability to replace cells of all those different tissues that are lost due to sickness or damage.[1] The use of IPSs in these specific chimeras, other than 'natural' pluripotent stem cells is essential to the importance and uniqueness of this technology, now it is a far less controversial choice than using human embryonic stem cells (hereafter: hESC) (a pluripotent stem cell for which one has to destroy embryos to obtain it), as is now often the case.

A very important aim of human-animal chimeras is to be finally be able to use them for growing and harvesting 'custom-made' transplantable human organs and tissue, thus solving the problem of the long waiting lists for donor organs. Further in the near future, it is expected that these chimeras are also of paramount importance in the study of organ formation and early embryo development, and will be very useful in medicine toxicity trials.[3] Even while some of these potential uses still have a lot of complications that need to be figured out before actual widespread use, it is important to define the (legal) position of this technology now. Whilst some of these uses might take years of further research before they can be realised, this is not freeing society from taking an informed stand and herewith either halter of support specific innovation.

It is undisputed that this combination of not only blending species, but also doing so by using IPSs is an enormous scientific breakthrough, which will in the long run not only change biotechnology, biomedical science, medical science and health care but also eventually the way we handle and value our bodies and how we arrange our lives.

With this new and promising technology at our hands, it is important to define its place in our current legal framework as human-animal chimeras have been raising ethical and legal concerns from the beginning of their discovery.

One of these ethical concerns is, for example, that research has gone too far by creating something so unnatural as a chimera, and that we should be afraid for the creation of some sort of animal with a human consciousness.

Closely linked to this is the moral argument that this kind of research is some form of 'hubris', 'playing God' so to say, and that some things should simply be left as they are.

Also, the fact that one needs to either kill or test on animals to conduct human-animal chimera research is considered an ethical burden. This debate sees mainly on the dilemma if it is morally justifiable to use animals as a mere mean, and only for our own

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[1] Yee, *Nature Education* 2010/3, p.25

[3] 'New findings highlight promise of chimeric organisms for science and medicine' *Salk* 26 January 2017, www.salk.edu

good.

Another possible ethical concern for many people could be that, before the invention of IPS cells, human embryos needed to be destroyed in order to obtain the hESCs that are needed to generate human-animal chimeras. With IPSs this will not be necessary anymore, and it is important to determine if this does indeed eliminate a main issue regarding human-animal chimeras or not. The fact that human-animal chimeras have been conceived as contrary to human dignity, is closely linked to the destruction of human embryos. This is because it is perceived by some that in order to create a chimera, one has to destroy (the potential to) human life.[5]

It is important to define these ethical concerns in relation to the technology, and analyse if the use of IPSs, or otherwise a different legal framework, could overcome these concerns. It should also be determined if the abovementioned concerns were of influence on the existing Dutch legislation, or if some of these aspects were of no importance when establishing the current legal framework in the Netherlands. Further in this research, the abovementioned concerns and dilemmas will be discussed.

Besides the ethical consideration, legal problems have arisen as well. Among others, there has been discussion about if and how laws covering human dignity and those laws protecting human rights would apply to the chimeras, since they partially consist of human cells, albeit in low percentage. A legal issue for researchers is also that research which makes use of hESC, is prohibited in various countries; therefore, the creation and use of human-animal chimeras is illegal in many States. Additionally, patentability has been an issue, which has been handled very differently all over the world, however for the scope of this research, this topic will not be discussed. However, when constructing an overall picture, it is important to realise that this is a legal issue as well. Safety and health regulations will also be briefly discussed, as this is also of paramount importance, concerning for example the spreading of viruses. Further, it is interesting to look if and how animal-welfare laws apply to this kind of research and medical use, and if these can be deemed sufficient to protect what we value.

It has been argued by several scientists, that these concerns and difficulties should not immediately lead to a complete ban of every possible creation, development and use of human-animal chimeras, since they have an enormous potential in, for example, regenerative medicine and other medical uses. However, since important and considerable objections can be raised, a solid legal framework is indispensable.

This paper aims to define the reasons behind the prohibition and restrictions that the creation and use of human-animal chimeras is bound by in The Netherlands. It will be determined whether the laws governing the creation and use of human-animal chimeras are driven mostly by concerns about the destruction of human embryos to obtain the necessary stem cells or by other (ethical) concerns. In the case of human-animal chimeras through IPSs, science has sidestepped the dilemma of the use of hESCs and the necessary destruction of embryos to obtain these cells.
This research seeks to clarify what underlying concerns the prohibitions and restrictions on the development and use of human-animal chimeras seeks to address. With the insights thus gained, the research answers the question whether or not the current prohibitions and restrictions in Dutch legislation are applicable to IPS-based chimeras and:

- if so, whether they can be relaxed and how that could be done, and

[5] Van Roermund, *German Law Journal* 2013/14, p. 1941

- if not, whether certain restrictions may need to be re-instated

The generating, development and use of human-animal chimeras is extremely auspicious, and now is the right time to specify the place of these creatures in our legal system again, focussing on the fact that the use of IPSs, other than embryonic stem cells, has expunged presumably one of the major objections regarding this technology. Soon, we will have actual living hybrids in our midst, and it is crucial to have a sufficient legal framework before they arrive. In an world were ground-breaking scientific developments take place everyday, it is of paramount importance to keep checking if the legal safeguards that we've put in place are still sufficient.

In this case science, as happens more often, found it's way around the letter of the law. Wu's team created an option that several jurisdictions never even considered in their drafting process, and as such had not integrated anything regard this option (creating human-animal chimeras through IPS) into their legal system.

Society now finds itself in an interesting position. Scientific development took away one of main ethical and legal burdens (the use of hESC) to continue chimeric research, as regarding Dutch legislation it can be argued that the current framework no longer prohibits the further development of human-animal chimeras when created through the use of IPS.

This paper will thus aim to determine the position of human-animal chimeras through IPSs (as discovered by Wu's team) in the Dutch legal framework, mainly focussing on their use in research and clinical medical use. Defined will be the legal restrictions and prohibitions governing the use and creation of the human-animal chimeras, and then investigated further, if these restrictions will uphold when there might no longer be a need to use embryonic stem cells to create a chimera. To come to this conclusion, the technology of chimeras and induced pluripotent stem cells on its own will be discussed, and then the combination of these two technologies will be compared to human-animal chimeras through embryonic stem cells.

This research will focus on Dutch legislation, where the further development of human-animal chimeras is strictly prohibited, unless - due a so-called legal loophole created by legislators who had not foreseen a technology like this - they are created through IPSs (or more specific, as long as they are generated without the use of hESCs). A closer look at this specific jurisdiction and its legislative history will hopefully provide some actual examples of the considerations that governed the current framework, and will show if the use of hESCs was really one of the biggest difficulties when drafting legislation concerning the technology of chimeras. To come to that conclusion, ethical and moral concerns regarding this technology will be discussed, and especially the influence these concerns had on the legislation.

Hopefully, it will be possible to conclude this research not only with a clear description of the position of the human-animal chimera in the current Dutch legal framework, but also with a benchmark in mind of how legislation should cover this particular new technology, keeping all the different technological, legal and moral aspects in mind.

Methodology

This paper will consist of a traditional legal analysis, using mainly Dutch national law to find the right answers concerning the position of the human-animal chimeras in the existing Dutch legal framework. National legislation and its legislative history, will be the main source of information to come to a sound conclusion regarding the legislative framework. That chapter is mainly based on the Dutch Embryo Act, the Special Medical Procedures Act, their legislative history and several letters from the Minister of Health, Welfare and Sport and the House of Representatives. Besides, the Evaluation on the Embryo Act and the Donor Data and Artificial Fertilization Act', published in 2012, was used.

Also, questions of morality and ethics can never be answered with the letter of the law alone. Besides the abovementioned fields, doctrinal research will have to be conducted in the field of bio-ethics, in this way providing the most inclusive description of this remarkable, yet controversial, technology and all its benefits and burdens. Several articles and reports of scientists, philosophers and bio-ethicists will be used to provide an overall view of the ethical concerns.

Besides the abovementioned research, doctrinal research into several scientific and biological subjects will be necessary to understand the facts of the complex, novel technologies that we face. Regarding the chapter explaining the technologies considered, mostly scientific papers, journals and researches from various scientific institutes and universities were used.

It goes without saying that these human-animal chimeras, their development and possible uses touch upon various aspects of our society, and it is therefor necessary to take information from diverse areas of expertise.

2. Technology Explained

To understand the underlying technology of chimeras and of IPSs, a brief explanation is necessary. First, the various chimeras will be discussed, followed by a brief explanation of the technology. Secondly, the technology of the IPSs will be discussed, especially their use in comparison with hESCs.

2.1 Human-Animal Chimera - Terminology

As mentioned above, a chimera is a creature consisting of different gene populations coming from different species.[6] With the development of technology, the term chimera has moved from defining a very imaginative creature in ancient Greek myths, to – in temporary scientific research – defining a creature consisting of cells of different genotypes. In modern day science, the term 'chimera' has been widely used in various scientific fields, and therefor the scope of what one can actually specify as a chimera is rather broad.[7] For example, since many years it has been a quite standard medical procedure for patients requiring a heart valve replacement to replace the human valve with a pig valve. In the field of medicine, this is considered a chimera.

Chimeras have also been defined as 'an individual, organ, or part consisting of tissues of diverse genetic constitution.'[8] As described above, a human with a pig valve qualifies as a chimera, but this research will focus on a different kind of chimera. The research focuses on the kind of chimeras which are created by inserting human cells into a animal embryo, therefore developing into a genetically novel creature, consisting of cells from two different individual organisms. This specific kind of chimera is the so-called embryological chimera.[9]

Also, besides the term chimera, one can also disguise two kinds of chimera research both with their own particular (ethical) concerns. The first kind of research concerns *in vitro* research (on early stage embryos) and the second kind of research concerns *in vivo* research (on sentient animals).[10] This research will mostly cover the *in vitro* chimera research, as executed by The Salk Institute in their mentioned research.

As mentioned, it is important to note that the various scientific fields that are involved with chimera research use a different explanation for the term 'chimera'. In this research the focus is placed on the embryological human-animal chimera, and the problems and concerns that rise with this specific kind of scientific research. This research will therefor follow the abovementioned definition, stating that a chimera is a '*combination of cells from different individuals*.'[11]

Concluding, chimeric research means in this case in vitro research, and a by a chimera is meant a creature consisting of different cell populations from different genotypes. For the sake of the length and completeness of this research, it will focus only on the legal and ethical aspects of human-animal chimeras through IPSs as generated in the research of Wu and his team, however it will often be in comparison to the human-animal chimeras based on hESC.

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[6] Taupitz, Weschka 2009, p. 5
[7] Bourret e.a., *Stem Cell Research & Therapy* 2016/7, p. 1
[8] *Merriam Webster* 2018
[9] Bourret e.a., *Stem Cell Research & Therapy* 2016/7, p. 1
[10] Hyun e.a., *Cell Stem Cell* 2007/1, p. 159
[11] Bourret e.a., *Stem Cell Research & Therapy* 2016/7, p. 1

2.2 Human-Animal Chimera - Technology explained

To fully understand the moral and legal challenges this technology creates, a certain level of understanding of the underlying, very complex, technological matters is essential. The following chapter aims to provide this basic knowledge, but due to the complexity of the technology at hand this explanation cannot be and aims not to be all-encompassing. It has to be kept in mind that the below explained technology to create chimeras through IPSs is at the moment the only successful attempt to create a human-animal chimera through IPSs on an embryological level. For understanding the concept of chimeras, the path followed by the Wu team is very briefly explained below. It is highly likely that in the near future other ways will lead to the same or a similar outcome, but for the sake of the length of this research the focus is on this particular manner to create a chimera.

As mentioned, this research will focus on human-animal chimeras created on a genetic level, which are created by injecting human stem cells into an animal embryo. This embryo is modified in such a way that specific genes will differentiate into the specific organs that are 'deleted', by using the so-called CRISPR-Cas-9 technology, from the embryo.[12] Very generally explained, if one wants to grow a human pancreas in a pig, the genes that are known to grow into a pancreas are removed from the pig embryo using CRIPSR. Once the human stem cells are injected into the pig embryo, the cells 'recognize' which genes are missing and will thus form into that particular organ.[13]

To create a human-animal chimera an embryo is cultured in vitro to the blastocyst stage, meaning that the embryo is around 5 days post-fertilization.[14] The Wu team then injected around 3 to 10 IPSs into the embryo with a very, very thin needle. After this stage, the embryos that were considered of high enough quality were transferred to surrogate sows. Collection of the embryos took place between day 21 and 28 of the development, collecting 186 embryos from the sow.[15]

Since the IPSs were marked with a fluorescent marker, it was possible to detect the ratio of human and pig cells in the embryos, thus confirming that chimeric development had taken place. It was further discovered that the IPSs differentiated into several cell types in the embryos.[16]

However promising this technology might be for a good deal of uses, it is not without severe technical complications, and the same accounts for the technology of IPSs itself, as will be discussed later. It is undeniable that a lot of work still needs to be done, and that further research is indispensible. Nevertheless, for the scope of this research, the enormous future potential is the most important. The technical complications and even the possibility that the desired outcomes of this research will never be obtained, should always be kept in mind, but should never be used as a reason to not discuss the position of this technology in the current legal framework.

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[12] Wu e.a., *Cell* 2017/3, p.475
[13] Feng e.a., *International Journal of Moleculair Science* 2015/3, p. 6550
[14] Wu e.a., *Cell* 2017/3, p 480
[15] Wu e.a., *Cell* 2017/3, p.480
[16] Wu e.a., *Cell* 2017/3, p.480

2.3 Induced Pluripotent Stem Cells - Technology explained

In the same way that chimeric technology is very complex, IPS technology is also quite hard to explain thoroughly. Again, for understanding the legal framework of these technologies, a basic comprehension of this technology is necessary. The following section shall aim to provide this knowledge with regard to IPSs.

The technology of IPS's is very recent, but, as mentioned, has been welcomed as one of the most important scientific inventions in decades. As will be extensively discussed further down, IPS's are stem cells, which are turned back to their 'original' state of pluripotency, therefor being able to differentiate into every kind of cell.[17]

In 2006 a Japanese lab of the Nara Institute of Science and Technology led by Shinya Yamanaka introduced the IPS technology to the world. They showed that it was possible to reprogram adult somatic cells into pluripotent stem cells, by introducing specific combinations of genes, which are associated with pluripotency, into the adult cell.[18]

Yamanaka, who has been awarded a Nobel Prize for his IPS research, knew that hESCs included transcription factors that had the ability to convert skin cells back into the embryonic state, and he decided to search for these factors in the cells. Starting from the genes in the nucleus of the cells (the cell identity, where all the genes are located), Yamanaka tried to discover if the once differentiated cells had to stay the particular kind of cell they developed in, or if they could change into another type again after their first development. He tried to make the stem cell return to its starting point, the pluripotent state in which differentiation into every kind of tissue was still possible. He tried to identify the transcription factors that are responsible for keeping pluripotent hESC pluripotent, hoping that these factors would turn back the clock for the already differentiated cells. With more than 100 possible factors, from which it was unclear if they would work together and if so in which combinations, it was going to take several years of work to find the correct ones that where responsible for the permanent pluripotent state of hESC. However, through the use of a computer program, it was possible to narrow the factors down to 24 possible transcription factors. Yamanaka decided to use four factors together, Oct4, Sox2, c-Myc and Klf4, now also known as the Yamanaka-factors. After inserting them into a skin cell, the chromosomes unwind and it was therefor possible for the factors to attach to the genes, which were no longer shielded by the chromosomes. It is important to note here that Yamanaka thus used a somatic cell, in this case a skin cell, to turn into a pluripotent cell. A somatic cell is *'one of the cells of the body that compose the tissue, organs and parts of that individual, other then the germ cells'.*[19] Yamanaka thus tried a cell that already differentiate into a cell which already has a specific task, back into a cell that could still differentiate into everything. The four added transcription factors could attach to the genes that were responsible for the production of embryonic proteins, therefor reprogramming the cell into thinking it was in an embryonic environment. During replication, the cells started to become similar to hESCs with every division, until they were completely alike to hESCs. The stem cell became pluripotent again, meaning it could be used to differentiate into any cell the human body has. Soon it was discovered that this did also work with every other somatic cell in the body, tremendously changing science's view on cell development forever.[20]

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17 Yamanaka, *Angewandte Chemie* 2012/52, p. 13904

18 Yamanaka, *Angewandte Chemie* 2012/52, p. 13905

19 *Merriam Webster* 2018

20 'Stem Cells - The Future: An Introduction To iPS Cells', *EuroStemCell Youtube,* 24 October 2012

Although very promising, IPS technology is still far from perfect. For example, it is known that some of the used transcription factors trigger certain onco-genes, thus creating tumours in the human body. For specific feature uses this is a challenge, but nevertheless, it should not withhold us from taking an informed stand about the possible future uses of this technology and the options it provides us in connection with scientific research.

3. Human-Animal Chimeras in Dutch legislation

The following chapter will define the position of the human-animal chimera in Dutch legislation, mainly focussing on article 25 of the Dutch Embryo Act (*Embryowet*) and article 6a of the Dutch Special Medical Procedures Act (*Wet op Bijzondere Medische Verrichtingen*). This chapter aims to provide an insight on the various reasons behind the establishment of these particular laws, especially focussing on the reasons for the (partial) prohibition on the creation of human-animal chimeras in The Netherlands.

As mentioned, the definition of chimera is rather broad, and several kinds of chimeras have existed in scientific research for a long time. This research however, focuses on the human-animal chimera on embryological level, and whenever chimeras are mentioned in law, it will be understood as mentioning these particular chimeras.

Furthermore, since the discovery of IPSs in 2012 certain parts of the Embryo Act have been up to debate, in particular the specific law mentioning human-animal chimeras. It was understood immediately that with the discovery of IPS new possibilities for the creation of chimeras had originated and that through the use of IPS technology the Embryo Act no longer prohibited the further development of chimeras.

By studying the reasoning behind article 25 of the Embryo Act and article 6a of the Special Medical Procedures , argumentation for the prohibitions and restrictions concerning the further development and use of human-animal chimeras will be determined. Hereafter, the consequences of the discovery of IPS for the existing legislation will be discussed. Several opinions on what to do next, now the existing Dutch legislation does not cover human-animal chimeras through IPS, will be discussed, hopefully leading to a clear outcome on the direction that is the best to be headed to in this case.

3.1 Article 25 of the Dutch Embryo Act

Article 25 of the Embryo Act is as follows:

> *Section 25*
> *The following procedures are prohibited:*
> *a. combining a human and an animal gamete with a view to creating a multicellular hybrid;*
> *b. allowing a chimera created from human and animal (or exclusively human) embryonic cells to develop for longer than fourteen days or implanting said chimera into a human being or an animal;*
> *c. implanting an embryo into an animal;*
> *d. implanting an animal embryo into a human being.*

Focussing on sub b of article 25, it is apparent that the creation of chimeras is not prohibited, but they cannot be developed past 14 days. The 14-days-rule finds its origin in an international agreement first proposed in 1979 by the United States, and later on endorsed by other countries. It was a result of the ethical discussions in the seventies following the first successful IVF procedures, trying to determine the moral status of the embryo. This, now decades old, rule has partly been based on trying to grant the human embryo some sort of moral status, as well as to not limit science too much.

An illustrative example hereof is the endorsement of the United Kingdom. In 1984 the UK recommended the proposal with the Warnock report, following the reasoning that after 14 days an embryo could not split in an identical twin anymore, therefor the embryo could be considered an actual individual. Even more, the reasoning behind this was that God could not have given an embryo a soul, as long as there was still a possibility that the embryo could split into two individuals. God would not give an individual soul to a creature that needed two souls, and after fourteen days the embryo

could no longer split therefor confirming its own individuality.[22] Besides this religious reasoning from the UK, more scientific reasons from scientists all over the world have supported the 14-days-rule and for years it has been international policy in several countries. It is now encoded in the national legislation of at least 12 countries, and can also be found in numerous guidelines for scientific research.[23] Nonetheless, especially over the past years this rule has been heavily criticized, because scientists are demanding a longer period of time to let embryos develop for the sake of science. However, for the time being, article 25b binds Dutch chimeric research to the 14-days-rule when hESCs are used.

It is important to note that implanting a chimera in either a human or an animal is at all prohibited. This will be discussed further below.

What is most important for this particular research is that the article explicitly mentions hESCs. It is prohibited to let develop further than 14 days or implant a chimera created from hESCs and animal cells in either an animal or human. Before Yamanaka's discovery, another option was simply not yet available to generate a chimera on embryological level.

It is important to define if the discovery of IPSs not only created a legal way to create chimeras, but if the legislators considered a chimera without the use of hESCs and deemed this something they wouldn't want to prohibit. Considering the strict letter of the law, the creation of human-animal chimeras through IPSs is legal, and researchers are even allowed to let develop this chimera longer than the mentioned 14 days. To find out if the only, or most significant, reason to prohibit the development of a chimera is the use of hESCs, one will have to take a look at the legal history of article 25b of the Embryo Act.

3.2 Legal history of article 25 of the Embryo Act

In 2002 the Dutch Embryo Act was adopted after careful consideration. In the Explantory Memorandum (*Memorie van Toelichting*) given by the House of Representatives the following reasoning regarding article 25b can be found.

Firstly the House of Representatives stated that there exists a broad scope of opinions and beliefs regarding anything embryo-related, from IVF to scientific research. For this reason, it has been impossible to find a consensus on a lot of subjects, but nevertheless a law was created to protect what the House of Representatives considered our most important values. They acknowledged that human dignity might be of such great value to some, that there will never be an argument significant and meaningful enough to breach this fundamental right in any way.[24] However, they further argued that for example, suffering as a result from childlessness, developing the quality of reproductive medicine in particular and medical science in general and the freedom of scientific research is of significant importance as well, and should be accounted for as well in the Embryo Act.[25]

Human dignity and respect for human life have been at the centre of all the decisions the House of Representatives took regarding this subject, keeping in mind that with an abundance of, often strongly felt, opinions on this subject a proper balance would be hard to find.[26] They've declared that, notwithstanding fully respecting human life, in some cases a breach of this principle is justifiable in the bigger context of life and

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[22] *The Guardian*, 6 May 2016

[23] Hyun e.a., *Nature* 2016/533, p. 171

[24] Parliamentary Documents II, 2010-2011, 32610, no. 3, p.3

[25] Parliamentary Documents II, 2010-2011, 32610, no. 3, p. 3

[26] Parliamentary Documents II, 2010-2011, 32610, no. 3, p. 5

all its facets. The House of Representatives then lists a couple of situations, which they considered to be an unjustifiable breach on human dignity, under any circumstance. The establishing of human-animal chimeras is one of them.[27] Given the fact that it is legally allowed to create a human-animal chimera and let it develop up until the 14th day, it can be assumed that with 'establishing' something past these 14 days is meant, and that only this was considered against human dignity.

Important to note here is that the House of Representatives does not give a reason for this prohibition, other than the statement that chimeras are considered contrary to human dignity. At the time the Explanatory Memorandum was written, to create a human-animal chimera on embryological level it was necessary to destroy a human embryo in order to obtain the necessary stem cells. The question rises thus if the destruction of an embryo was considered contrary to human dignity, or that the creation (and more importantly, further development) of a human-animal chimera itself was considered contrary to human dignity. Concerning the fact that it is legally allowed to create human-animal chimeras on embryological level, but not to let this embryo develop past 14 days, it seems that the destruction of the embryo is not the main reason the House of Representatives prohibited the establishing of chimeras.

For other proceedings with regard to the use and creation of embryos, conditions apply. First, the purposes of the use of the embryos should be limited, focussing on only important causes, alike the welfare of childless couples or finding a medical solutions for specific diseases. Secondly, the use for these purposes should be bound by limitations as well. For scientific research, this could mean consent of the donor and compliance with specific legal requirements concerning research.[29] In the light of article 25b of the Embryo Act, this regime of conditions as described above, applies to the creation of human-animal chimeras and letting them develop up until the 14th day.

The House of Representatives took into consideration the possibility of future further scientific developments, but still stated that some things will always be contrary to human dignity, including the further development of chimeras past the 14th day.[31] The House of Representatives also stated that further development past 14 days must be considered highly unlikely.[32]

Concluding, the Explanatory Memorandum does not provide actual arguments, rather than the fact that it prohibits something because it is deemed to be against human dignity or is deemed to not respect human life. Both are rather broad concepts. Under article 25b of the Embryo Act it is possible to generate chimeras, thus the law does not prohibit per se the destruction of human embryos for scientific purposes, however, be it under very strict conditions.

Fast forward to 2012, where Yamakana's discovery shook the scientific world on its foundations. It was immediately clear that the possible replacement of the use of hESCs in scientific research could be one of the biggest advantages of this invention.

Already in September 2012 the 'Evaluation on the Embryo Act and the Donor data and Artificial Fertilization Act' (*Evaluatie van de Embryowet en wet donorgegevens en kunstmatige bevruchting*), written by the Dutch Organisation for Health research and Healthcare innovation (*Nederlandse organisatie voor gezondheidsonderzoek en zorginnovatie*), was published. It acknowledged the great importance of IPS in future medical scientific research, and its possible impact on regenerative medicine. In the rapport it is mentioned that article 25b of the Embryo Act does not apply to chimeras generated with IPSs, as

27 Parliamentary Documents II, 2010-2011, 32610, no. 3, p. 6
29 Parliamentary Documents II, 2010-2011, 32610, no. 3, p. 6
31 Parliamentary Documents II, 2010-2011, 32610, no. 3, p. 47
32 Parliamentary Documents II, 2010-2011, 32610, no. 3, p. 47

the article specifically mentions hESCs, and therefor asks for clarification on the scope of the article after the discovery of IPS. The rapport explicitly and mainly mentions the possibility of growing human organs in animals, and points out the apparent legal lacuna. It concludes stating that the possibilities of growing human organs in animals are of such promising nature, that a complete ban or even the old strict 14-days-rule might be too rigid.[33]

The rapport then focuses on the different kinds of objections the legislator could have with the abovementioned technology. It mentions human dignity and animal welfare as important matters to take into account, and to keep in mind the moral objections one could have with the technology once the IPSs start floating around in the animal embryo. It is suggested that this might lead, for example, to an adjustment in the brain, giving the animal cognitive functions similar to those of humans. However, the rapport immediately states that those chances are extremely small, and that these events are, according to scientists, at all times preventable.[34] With regard to animal welfare in relation to this particular use concerning human-animal chimeras, the rapport is very clear. There are certainly moral objections concerning the sacrifice of animals for science, but there are unquestionably reasons to justify this. It further states that the this use of human-animal chimeras would also fall under the scope of several national animal welfare laws, and that a license from the Committee Biotechnology at Animals (*Commissie Biotechnologie bij Dieren*) should be obtained. Moreover, it is reconfirmed that with the development of these technologies further discussion on moral and ethical aspects of chimeras is indispensable.[35]

The recommendation the rapport gives concerning the Embryo Acts is as follows. Firstly, the legislator should clarify whether article 25b of the Act does apply to human-animal chimeras through IPS that are placed in the womb of an animal. If indeed the scope of the article was meant to include this, and therefor prohibit it, the rapport suggests that the legislator should consider if this is not too restrictive, keeping the very promising possibilities of human-animal chimeras in mind, herewith mainly focussing on the growing and harvesting of human organs. It further suggests that if the legislator does not consider human-animal chimeras through IPS to fall under the scope of the article, it should consider if it is necessary to regulate this technology through other new legislation or means, as it now mainly unregulated[36]

It is important to note that the rapport primarily focuses on the one specific use of a chimera, namely that of growing human organs. The rapport demands clarification concerning the scope of article 25b, but mainly in the context of this specific use of growing organs. Further, it also seems that the tone is in favour of this new technology, as the rapport tries to refute some objections the legislator might have concerning animal welfare and potential negative effects of the technology. Also, the recommendation itself emphasizes again and again the potential importance of the technology, and the importance of enough legal leeway for scientific developments.

July 2013 the Minister of Health, Welfare and Sport sent a letter to the House of Representatives, in reaction on the abovementioned Evaluation of the Embryo Act (2012). Most importantly, she agreed with the evaluation that IPSs cannot be considered hESCs, and that the scope of the article was never meant to be that far reaching. However, she stated that the meaning behind article 25 was always to limit the creation and development of human-animal combinations. The discovery of IPS does not change

[33] Evaluation Embryo Act 2012, p.195
[34] Evaluation Embryo Act 2012, p. 195
[35] Evaluation Embryo Act 2012, p. 195
[36] Evaluation Embryo Act 2012, p. 240

this. The Minister added that she is not blind for the enormous future potential, but she considers the technology to be in a too early stage to already abolish the prohibition on development past the 14-day-rule. She concluded with the message that she had the intention to change the existing legislation so that it would also prohibit the further development of human-animal chimeras through IPS, but that she would closely follow any developments regarding this technology so it could be decided later on to reverse the prohibition.

Dutch scientists, from whom some of them were also involved in the Evaluation of the Embryo Act (2012), reacted to the letter of the Minister. They responded that the technology was by far too underdeveloped to be prohibited right away, and that it was perfectly possible that major objections would disappear over time with the development of the technology. At least, the technology should be considered still in its infancy, and could not cause any harm yet, if it would ever do so at all. They also argued that it could be considered harmful for national scientific research to only look at foreign developments, instead of also taking part in this research, and to only base politic and legal decisions on those outcomes. It was further suggested that it might be very difficult to reverse an existing legal prohibition.[37] Again, in the same slightly optimistic tone as the Evaluation of the Embryo Act (2012), it was suggested to wait a bit longer, and to watch the developments closely to decide if the strong objections that there were regarding this technology would really uphold.

It can however be argued that this argumentation overlooks the possibility that one could already have strong objections against this technology, regardless of the stage of development of the technology. Further, it also overlooks that if no legislative framework is in place, and further development would be allowed, after successful tests it might be harder to prohibit the technology – even thought the moral objections have not yet been taken away.

Up until the writing of this essay, article 25 of the Embryo Act has not yet been amended.

3.3 Article 6a of the Dutch Act on Special Medical Procedures

Article 6a of the Special Medical Procedures act sees on xenotransplantation, which can be defined as '*the transplantation of an organ, tissue or cells between two different species.*'[38] However, the definition as used in the above paragraph is narrower then the definition as used in the Special Medical Procedures Act. Xenotransplantation is defined in Dutch law as the introduction or application of living components of an animal or of a fetus or embryo of an animal, or a human component that has been purposefully brought into contact with it, in or on the body of a human being.[39] It is important to note that article 6a does not refer to chimeras, and also not to every possible use of the chimeras. However, it prohibits implementing a human component that has been purposefully brought into contact with living components of an animal, into the human body. This article most likely prohibits the introduction of an organ, grown in an animal, into the human body. It therefor blocks the use of organs from chimeras for human patients in need of an organ, but it does not prohibit the further development of chimeras.

In the Explanatory Memorandum of the amendment of the Special Medical Procedures Act from 2002 the background of the forbiddance of xenotransplantation is explained.

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37 *NRC* 26 September 2013

38 *Merriam Webster* 2018

39 Article 6a of the Dutch Special Medical Procedures Act

It can be argued that xenotransplantation did not lived up to the expectations that existed when xenotransplantation seemed to be a legitimate option to solve the problem regarding the long waiting lists for organs. However, years later science has not yet found a way to overcome one of the biggest hurdles of xenotransplantation, namely that of contamination of the receiving person with transmissible viruses coming from the donor animal, and further the transmission of endogenous retroviruses.[41] The Explanatory Memorandum lists these abovementioned disadvantages as the two biggest reasons why xenotransplantation has been put on a hold. The most compelling reasons are thus the possible risks a patient would be exposed to, and subsequently the possible damage it could do to public health. There is no mention of 'human dignity' nor are there any ethical objections that are raised regarding xenotransplantation. The Minister even mentioned that as soon as these health and safety issues are solved, the legality of xenotransplantation should be considered again, as it should be regarded as a very promising technology.[42] However, as mentioned before, these safety issues have not been solved yet, and it is not likely they will be solved in the (near) future. Xenotransplantation in the 'classic' way will therefor probably stay prohibited, as long as the worries regarding health and safety stay valid – and they have up until now.

As is mentioned in the Explanatory Memorandum, the only – or at least the only mentioned – objections thus regard safety measures and (public) health. When these concerns can be taken away the Minister states that she does not see any reasons to further halter this development. The generation of chimeras through IPS is not xenotransplantation in the way as is meant in the Special Medical Procedures Act, as again the legislator had not foreseen this technological possibility. Nonetheless, the fear of cross-contamination of viruses can also apply to the organs harvested out of chimeras. However, circumstances are now different regarding a very important aspect, as the organs are made out of human cells.[43] Besides the doubts about the possibility of growing organs in animals, safety concerns are the biggest complication. It is therefor that the then existing critic regarding (public) health has not yet been refuted, but options such as a sterile living environment for the animals have been mentioned.

3.4 Further remarks on the existing legal framework

The following conclusions about the current legal framework can be drawn. The use of hESCs seems, however not undisputed, not a compelling enough reason to not generate human-animal chimeras. Following the Embryo Act, researchers were already allowed to do so to create chimeras, but they were just not allowed to develop those chimeras past 14 days. The ethical dilemmas that rose by using hESC are neither mentioned in the Evaluation nor by the Minister. The real problem seems to be the further development of the chimera, developing past the 14-day rule so to say, and the possible further uses of this technology. The actual creation, using hESC or not, does not seem to be the problem with regard to the chimera.

The Explanatory Memorandum of the Embryo Act stays rather vague about the possible objections regarding further development, mentioning only briefly aspects such as 'contrary to human dignity', without going into further detail as to why this technology should be conceived so, and what should be considered important aspects of this human dignity. Regarding article 6a of the Act on Special Medical Procedures, ethical considerations are not even mentioned in the Explanatory Memorandum, as the main concerns are clearly health and safety aspects.

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[41] Shaw, *Bioethica Forum* 2014/7, p. 24
[42] Parliamentary Documents II, 2001-2002, 28284, no. 3, p. 2
[43] Shaw, *Bioethica Forum* 2014/7, p. 25

Maintaining both article 6a of the Act on Special Medical Procedures and article 25a the Embryo Act, will create a situation were chimeras can be generated and further developed, however the organs that grow inside of these chimeras can not be used legally for medical means. However, chimeras can still be really valuable for the scientific world and medical research, as these chimeras can be used for generating in vitro medicine screenings and disease models. It can further be used to study the growth process of human organs. However, as mentioned above, the transplantation of these organs will most likely be deemed illegal under art. 6a of the Special Medical Procedures Act.

Regarding the existing framework, it should be noted that there are several other fields of law that in some way also connect to the creation, development and further clinical use of chimeras. As mentioned above, animal rights and strict health and safety laws govern any research conducted with animals, and strict regulation regarding scientific research is in place anyway.

Something that should also be considered is if animal welfare laws and laws governing animal research would be sufficient once these chimeras do exist, since they are not wholly only animals. If an animal holds human organs, is it sufficient that the only laws protecting this pig are the laws governing animal welfare? Do we consider chimeras as animals only? Since they are two blended species, it might be argued that the laws governing them should not be the laws that were meant for only one of those species.

Another, even more complex but closely linked, discussion is the debate about the validity of fundamental human rights in this case. Besides the concept of human dignity in connection to the concept of creating human-animal chimera, it is also important to determine if these human rights would also apply to the chimeras that would be a result of the further development. After all, these creatures would be partly human, be it in low percentage. Can we thus consider, as mentioned, animal rights sufficient?

Human-animal chimeras challenge our perception of what we consider to be human, and what we consider to be human enough to be worthy of protection by our fundamental rights. Should we aim for protecting something as soon as it consists of some human cells, or is an actual human being something more?

These questions can not be answered here, not only for the sake of the length of this research, but also because this discussion really comes down to: 'What do we consider human?', and an ethical question like that might never be answered in a satisfying way – nonetheless we will shortly address this point further below.

Also, considering the lacking general consensus about human-animal chimeras in general, it can be argued that their status (human or animal) might be up to debate as well. It is however important to mention these consideration, as more than anything else, it points out the need for a strong legal framework as several important aspects are now unregulated, leaving ethical dilemmas up to the scientific world.

Another complex legal aspect about the human-animal chimeras through induced pluripotent stem cells that should be kept in mind, is that the Embryo Act was based on very heavy ethical considerations. The decision to prohibit the further development of human-animal chimeras has been thought true intensively, trying to do justice to all kinds of interests that are connected with this technology, as is described in the Explanatory Memorandum. Regardless if the decision at that time is right or not, it was a decision taken by a democratic government, after consultations of several experts in various

fields. However, as happens more and more often, the development of technology overtook the letter of the law, therefor bypassing a certain restriction the legislator made. Now the technology is developing even further, it is important to define if the development that it went through is enough to discard the objections that the legislator had with the earlier version of human-animal chimeras, or that these prohibitions still uphold.

4. Human-animal chimeras through induced pluripotent stem cells in Dutch legislation

After determining the current status of the human-animal chimera on the basis of hESCs, it is important to try and define the aspects, which are important to take into consideration when amending the current legal framework (if necessary). First, the position of the human-animal chimera through IPS in the current legal framework will be discussed by pointing out provisions of Dutch law that govern this technology, and by determining if this can be deemed sufficient. Second, the ethical considerations regarding human-animal chimeras will be discussed, as these are important when drafting legislation that will be accepted by the public. Lastly, a more general aspect of law regarding new technologies will be discussed, to identify the more general problem of out-dated law and fast developing technologies.

4.1. Legality of human-animal chimeras through induced pluripotent stem cells

As mentioned above, the Embryo Act and the Special Medical Procedures Act have not yet been amended. Both the Evaluation from 2012 and the subsequent letter of the Minister confirmed that article 25 of the Embryo Act does not cover, nor did intended to cover, human-animal chimeras through IPSs. Human-animal chimeras through IPSs are something completely novel and do therefor not fall under the current legal framework. The Minister has been aware of this since at least 2012, as the Evaluation has been very explicit about this. Since then, no new laws explicitly regulating human-animal chimeras through induced pluripotent stem cells have came into force.

Regardless of the firm words the Minister wrote in her letter of 2013, expressing her will to prohibit human-animal chimeras through IPSs, it seems that in reality a more nuanced position on this subject has been taken. In March 2017 two essays commissioned by the Ministry of Health, Sport and Welfare on the ethical dilemmas concerning growing human organs in animals was published. These essays, 'Growing human organs in animals: an ethical discussion' (*Menselijke organen kweken in dieren: een ethische discussie*), highlighted the two sides of the coin. On the one side, researchers, who were also involved with the Evaluation from 2012, expressed their concerns regarding a prohibition. On the other side, a Professor by special appointment on Christian Philosophy discussed his view on the ethical aspects of human-animal chimeras.[45] These essays will be discussed more detailed below, as they are of great importance when discussing the ethical dilemmas concerning this invention, but do not see on the legality of it. However, the commissioning of this research by the Ministry shows that further and more in depth considerations are deemed necessary to decide on how to pursue with this complex topic in terms of the law.

For now, it can at least be argued that the generating and development of human-animal chimeras through IPSs is not explicitly covered by existing laws. It has not (yet) been prohibited, and a final position has yet to be taken by the legislator. However, as mentioned above, this does not mean that there are no rules in place at all. Existing animal welfare laws and strict regulations concerning health and safety are in place when it concerns anything related to testing on animals or biotechnological research. However, these regulations will only govern in part how we arrange research and how to treat chimeras as soon as they are here – at least if we consider them to be animals. The

[45] Jochemsem, Dondorp & de Wert 2017, p. 2

current legislation was however clearly not drawn up with chimeras in mind, and will therefor most likely not provide an inclusive legal framework, since new ethical dilemmas originated.

It can be argued that these laws that regulate certain aspects of the technology, but not the technology explicitly, are not sufficient in the long run. Since this technology does not only has the potential for several future uses that could drastically change medical treatments, it also could potentially safe the life's of thousands of people that are now on the waiting list for an organ transplantation, and could provide useful and necessary insights on organ development and regenerative medicine,

It is highly imaginable, and also understandable, that the Minister was simply awaiting the development of the technology at hand. As soon as the benefits have become reality, and are not only a future possibility anymore, it is likely that the creation and use of human-animal chimeras will find remarkably less resistance from the public, therefor making it a more favourable action to regulate. It can be argued, as human-animal chimeras are now still quite controversial, it might be quite a political risk to take a definite stand on this topic. This however does not, and does never, excuse the legislator from its task to make sure appropriate legislation is in place. The grey, in between, area that human-animal chimeras now fall under is therefor not sustainable for much longer, maybe one of the only things the proponents and the opponents agree on.

4.2 Ethical considerations regarding human-animal chimeras

The abovementioned essays from March 2017 set out several ethical considerations regarding human-animal chimeras, more specifically the growing of human organs in animals. These considerations should be kept in mind when further examining how human-animal chimeras should be regulated. Firstly, professor by special appointment on Christian Philosophy, Henk Jochemsen, discusses the ethical concerns. Shortly summarized, his argument is as following: he fully acknowledges the importance of the technology with regard to improving health of patients, saving the lives of those on the waiting list and the importance for research.[46] However, he stresses that the feasibility of the techniques is still very, very unclear and further mentions that it can be considered unfair to spend remarkable amounts of money and time on a solution that might only serve a small amount of people. This is substantiated as the principle of subsidiarity, which means, according to Jochemsen, to find out if there is a similar technique, which solves the same problems, but with less (ethical) concerns and disadvantages. Also he argues that there are diseases that affect by far more people, and therefor might deserve the attention and available budget more.[47] Secondly, he discusses the ethical objections as mentioned in literature. He follows the analysis of Robert Streiffer, Associate Professor in Bioethics and Philosophy at Stanford, regarding the objections and concerns people have with human-animal chimeras. Streiffer mentions the following arguments on which, according to him, the chimera discussion is focussed: the Unnaturalness Argument, the Moral Confusion Argument, the Borderline Personhood Argument, the Human Dignity Argument and the Moral Status Argument.[48] Streiffer thus provided a framework in which chimeric research should be addressed in public policy.[49] These arguments will be briefly explained below, and will be, where possible and necessary, complemented with aspects of the Dutch situation.

[46] Jochemsem, Dondorp & de Wert 2017, p. 5
[47] Jochemsem, Dondorp & de Wert 2017, p.6
[48] Streiffer 2015, p. 1
[49] Streiffer 2015, p. 1

The Unnaturalness Argument focuses on the crossing of the natural boundaries of species. Simply because an organism is not natural, it should be considered unethical. Arguments against this theory focus on two aspects. Firstly, the whole concept of what a species is, and how over time fusion of species (without human interference) can take place. Crossing the boundaries of different species might therefor be not so unnatural after all. Fixed boundaries as such might simply not exist, as they do change over time anyway, and we can therefor not account any moral relevance to them.[50] However, Jochemsen argues that only because some exceptions exist (for example, he mentions a lion and a tiger, which together can have offspring), this does not mean that it can be considered natural. He argues that the exception just might prove the rule, and that fixed boundaries therefor do exist.[51] Besides the argument that cross-boundary species are not necessarily unnatural, another argument might be that unnaturalness does not imply by definition wrongfulness. The fact that something is 'natural', whatever that may be, does not make something good or just. It also implies that anything that is manmade cannot be considered 'natural'. If one takes this line of reasoning further, then nothing that is manmade is natural, and only that what can be considered natural is good, therefor nothing humans do is good.[52] That chimeras are wrongful because they are unnatural is not an argument that the Minister mentioned in her letters concerning this subject, but it is highly likely that this might be a concern that the general public would have regarding any new technology. According to Jochemsen, this is a very common reaction towards new technologies.[53] He also mentions that the Unnaturalness Argument entails more points of discussion. It embodies the fear of people to deliberately change the natural order, to create something that will change the world as we know it for the worse.[54] Jochemsen also focuses on the relation between the reactions of the public and morality. He argues that by simply stating that the abovementioned considerations are only emotions the public should overcome, one does not assign enough value to the emotions of the public. Jochemsen states that emotions substantiate moral standpoints, and are an outcome of the moral considerations of the public. It is therefor important to also take the supposed human resistance against unnaturalness, or the fear of hubris, or the fear to break the natural order, into consideration, as it embodies the underlying moral believes of the public.[55] However to create a legal framework in a democratic society regarding something very new that might unease many people, emotions should not – even if they embody the moral standpoints of the public - be guiding. Jochemsen argues to give serious weight to possible ethical concerns of people, but as Streiffer already argued and is mentioned above, this argument does not hold for various reasons. A scientific point of view would most likely be that fear of the unknown is not a valid reason to halter technological development, wheras Jochemsen argues that these emotions are very valuable and show us what we truly consider amoral – and that this should be considered enough reason to try and find another way around this technology.

The second argument Streiffer mentions is the Moral Confusion Argument. This argument suggest that people object to chimeras, simply because they are confused by their existence. Human beings have a full moral status, with all rights and obligations that come with this. With regard to chimeras it is still unclear how we could define them, and if and to what extend we should consider them human. It is very difficult to decide which legal framework one should apply, as we've discussed before. Streiffer mentions

[50] Streiffer 2015, p. 5
[51]Jochemsem, Dondorp & de Wert 2017, p. 18
[52] Streiffer 2015, p. 7
[53] Jochemsem, Dondorp & de Wert 2017, p. 19
[54] Jochemsem, Dondorp & de Wert 2017, p. 20
[55] Jochemsem, Dondorp & de Wert 2017, p. 20

the example of biomedical research in the case of chimeras, questioning which research protections should apply: those meant for animal research or the more protective rules for research on humans? This confusion threatens the social structures that tie our society together, which is partially based on a clear distinction between human and nonhuman creatures.[56] Streiffer then quotes an argument from 'Part-Human Chimeras: Worrying the Facts, Probing the Ethics' from Jason Robert and Fracoise Baylis, that "*the creation of novel beings that are part human and part nonhuman is sufficiently threatening to the social order that for many this is sufficient reason to prohibit any crossing of species boundaries involving human beings".*[57] Streiffer however, argues that it is highly unlikely that chimeras may cause confusion, as no research up until now has proven so, and that even if they would cause any confusion, this should not be considered sufficient reason to prohibit them. Streiffer states that chimeras which are hard to classify, as either human or nonhuman, are purely hypothetical, as up until now even the highest level of mixing resulted in completely obvious nonhuman creatures.[58] Streiffer ends his reasoning on the Moral Confusion Argument, with that *'to prevent scientific research on the grounds that it would force people to re-examine our views about moral status, would be to prevent not only scientific progress but urgently needed moral progress as well."*[59] Again, when constructing a legal framework it is important that society defined where in this framework they want to fit the chimeras. Streiffer argues that there is little chance that someone would be confusing regarding the existence of a chimera, however as soon as a pig might be carrying the organs a person might desperately need, it is easily imaginable that someone would prefer a stricter framework to protect the chimera. The answer to where the chimeras should be placed in the legal framework, and how they should be protected does therefor need specific consideration.

The third ethical dilemma is the Borderline Personhood Argument. This is a very specific argument, as it only considers chimeric research on Great Apes. David DeGrazia applied traditional animal ethical research in the context of human-ape chimeras. He argues that Great Apes could be considered 'Borderline Persons', as they display certain characteristics that should grant them full, or near full, moral status.[60] DeGrazia substantiates this argument very detailed, however for this specific essay it is foremost important to take into consideration that different animals need a different legal framework. However, Dutch legislation takes this argument already into account, as biomedical research on Great Apes has been prohibited since 2003.[61] The underlying fear substantiating this argument is most likely focusing on the possibility that a chimera (accidently) would begin to show human treats, emotions or similar cognitive functions. As Great Apes already are considered close to the human species, this would create a species that we could most likely not consider mainly animal anymore. This fear is also closely linked to the abovementioned Moral Confusion Argument.

The fourth argument is the Human Dignity Argument. As already mentioned, human dignity was one of the reasons why the Minister decided to prohibit (the further development of human-animal chimeras in the Netherlands, however without further explaining what human dignity entailed in this particular situation. Streiffer reasons that to assess human dignity and human-animal chimeras, it firstly should be decided what human dignity is, then to decide which individuals can claim human dignity and lastly to define what kind of implications and consequences this moral status really brings.[62]

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[56] Jochemsem, Dondorp & de Wert 2017, p. 20
[57] Baylis, Robert, *The American Journal of Bioethics*, 2007/7, p. 42
[58] Streiffer 2015, p. 12
[59] Streiffer 2015, p. 12
[60] Streiffer 2015, p. 14
[61] Parliamentary Documents II, 2002-2003, 28503, no. 4, p. 2
[62] Streiffer 2015, p. 15

Streiffer states that *'Human dignity is grounded in the possession of certain morally valuable cognitive and emotive capacities, and it is because these capacities are valuable that individuals with human dignity are themselves valuable.'*[63] Further, briefly summarized, he mentions that the moral implications that follows from having human dignity, is that one should not wrong those 'morally valuable dignity-grounding' capacities.[64] To highly simplify his statement: do not in any way harm or damage those valuable capacities that make someone an individual. Jochemsen takes a different stand on what human dignity is. He argues that human dignity is an intrinsic qualification, connected to the mere fact that one is a human being, irrespective of their other capacities or characteristics.[65] Jochemsen argues that these different views on what should be considered human dignity will affect public policy about chimeras. His view makes a clear distinction between humans and animals, but Streiffer's view is based on qualities and capacities.[66] Further developing of human-animal chimeras, especially those chimeras that will have affected cognitive capabilities, more humanized to say so, will raise different questions concerning human dignity, depending on which view is maintained.

The fifth and last argument is that of The Moral Status. In summary, this argument focuses on what happens after society grants the chimera a higher or full moral status. For example, if one should consider a chimera to have full moral status, it can be argued that chimeras could no longer be used or generated for the purposes we now imagine, such as research purposes. It is therefor important when drafting a legal framework, and considering the moral status of the chimera, that this classification will have a direct effect on its 'usefulness' for society. The use of chimeras for our own ends can in no way be reconciled with a higher moral status. The legal framework applying to chimeras will therefor largely be based on the moral status that will be granted to the chimeras by the law. As soon as this comes close(r) to the moral status of humans, this will change how and if research can take place.

Wybo Dondorp, Associate Professor of Biomedical ethics at the department of Health, Ethics & Society of Maastricht University, and Guido de Wert, Professor of Ethics of Reproductive Medicine and Geneticism at the Faculty of Medicine of Maastricht University, wrote an accompanying essay to that of Jochemsen. It also highlights the possible ethical consideration and objections that should be taken into account when drafting a legal framework, but it is definitly more tilted towards finding a solution in adressing possible objections without losing the medical possibilities that the generating and use of human-animal chimeras entail. Their essay is dividided into three main concerns. Firstly, it is adressed if the generating and use of chimeras should be defined as misuse of animals. Secondly, if human-animal chimeras really should be considered an unacceptable intervention into nature, and lastly they discuss if human-animal chimeras are against human dignity. Dondorp and De Wert do not follow the ethical framework of Streiffer as Jochemsen did, but many of their arguments fit in there as well. The combination of the two essays therefor embodies a considerable amount of the possible objections and views thereon, laying bare the difficulties of creating a legal framework.
The first possible objection Dondorp and De Wert analyse sees mainly on animal welfare. Their analysis is thorough, but can be summarised as follows: It is important to substantiate what it means for the welfare of an animal to be brought into this world as a chimera. It is indeed inevitable that chimeras will lead atypical lives for their species, but Dordorp and De Wert argue that this counts for all animals used for research, and even

[63] Streiffer 2015, p. 15
[64] Streiffer 2015, p. 15
[65]Jochemsem, Dondorp & de Wert 2017, p. 11
[66]Jochemsem, Dondorp & de Wert 2017, p. 13

for, for example, a dairy cow. Chimeras will, hopefully, be used for organ harvesting, but they will also be of paramount importance for medical and scientific research. Dondorp and De Wert are very clear on this subject: there is indeed an international aim in the scientific world to use as less testing animals as possible, however only when there is a sufficient alternative. Concerning organ development, this is simply not (yet) the case, and the use of actual animals is therefor necessary. Dondorp and De Wert further emphasize that the potentially enormous amount of information and knowledge this research will provide, does compensate for the use of test animals.[67] They also touch upon the instrumentalisation of animals, as all of them would live in particular sterile environments and then be killed for human ends. They do not provide an actual argumentation as to why this would be acceptable or defendable, but rather argue that society has always used animals for their own good. They argue that as long as animals are killed simply only for food, there can be no possible objection against growing an animal (only) to kill it for its organs.[68] It might be more substantial to follow the same line of reasoning concerning test animals here as well, meaning that there is simply no other comparable option that is just as useful for organ-creation or scientific research.

Dondorp and De Wert also, just like Streiffer building upon Degrazia, touch upon the possibility of human-ape chimeras. They describe the paradox concerning the use of primates for animal testing, as the results will most likely be the closest to testing on human, however this resemblance also raises even more ethical considerations, regarding that their feeling and understanding of pain might be very similar to that of humans. They follow the reasoning of Degrazia, that Great Apes should never be used for any chimera research, even if this would mean that organ harvesting through chimeras would never be possible.[69] However, as mentioned, animal testing on Great Apes is prohibited in the Netherlands, so this possibility is already legally excluded. It might be worth considering how one would want to define other categories of primates, as only the chimpanzee, bonobo, oerang-oetan and gorilla are mentioned, so other categories of primates are still, be it only when there is no other option, used for research.[70] Dondorp and De Wert do not per definition rule out this future possibility.

The second argument sees on the intervention with nature, and the so-called natural order of things. Referring back to Jochemsen's essay, this argument sees on that what should be considered natural, or what we perceive as the natural order of things. Dondorp and De Wert link this argument directly to religious argumentation, but this might be a too narrow group.[71]Concerning the natural limitations humans should respect, Dondorp and De Wert are very clear: natural limitations are no moral limitations. The fact that something does not occur in nature does not in any way imply that it should be considered immoral.[72]

Dondorp and De Wert state that the argument that something is natural has a strong rhetoric function, but that is also provides us a handhold in modern day society. The distinction between animals and humans is an important one, because it also defines us as humans. If humans and animals start to blend into something new, it challenges our perception of what we should consider human beings or animals.[73] Disrupting technologies challenge our worldview, and it is therefor safer and easier to rely on a 'natural order' argument, if there is even such a thing as a natural order.

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[67]Jochemsem, Dondorp & de Wert 2017, p. 66
[68]Jochemsem, Dondorp & de Wert 2017, p. 67
[69] Jochemsem, Dondorp & de Wert 2017, p. 69
[70] Article 10 sub 1 of the Dutch Law on Animal Experimentation
[71] Jochemsem, Dondorp & de Wert 2017, p. 70
[72] Jochemsem, Dondorp & de Wert 2017, p. 70
[73] Jochemsem, Dondorp & de Wert 2017, p. 71

Like Jochemsen, Dondorp and De Wert also pay attention to emotions the public might feel towards a new invention. They mention the concept of 'the wisdom of repugnance', coined by Leon Kass. This concept, which is closely related to the idea of the 'yuck-factor', encompasses the idea that when people have a deep feelings of repugnances towards something, this must be the *'expression of deep wisdom, beyond reason's power to fully articulate it'.*[74] Dondorp and De Wert argue that deep-rooted repugnance as a reason to stop and rethink certain developments is not necessarily a wrong idea. However, it should always be carefully defined upon what this negative feelings are based. Does it concern animal welfare or possible complications for the people involved? What is the origin of these feelings of repugnance, and does it indeed protect us as some sort of wisdom, or is it only haltering technological development? Is indeed something like that, or is that repugnance based again on the fear to break the perceived natural order of things?[75]

Dondorp and De Wert also refer to the 'species'-argument, that it is against natural order to blend species. They also argue that the whole concept of 'species' is not as clear-cut as opponents of human-animal chimeras often describe. Dondorp and De Wert mean that, more then disrupting a natural order or erasing a line between a natural divide between species, chimeras change the moral notion that society has of species. As Streiffer, following Robert and Baylis, already mentioned, the whole concept of a species is important for how we arrange or lives and relationships, *'in the way we live our lives and treat other creatures, whether in decisions about what we eat or what we patent.'*[76] It is therefor not a natural order we disrupt by creating chimeras, but or own social construct of limitations between species.[77] However, it might be worth considering why this could not also count as an argument against generating chimeras, maybe even more so than an argument based on perceived naturalness. If something does indeed challenges (and maybe even destroys) the social constructions society builds its daily life around, why cross that line? Or, should one follow the reasoning of Streiffer, that by the refusal of technologies that challenge our moral perception, we deny ourselves moral progress.

The third, and last, argument of Dondorp and De Wert sees on human dignity. They make the same divide between definitions of human dignity. On the one side there is this idea that human dignity is something that is inextricably linked with being a human. The second category connects human dignity to a set of cognitive and emotive capabilities. Dondorp and De Wert fully acknowledge the fact that in a society like ours, with a plethora of different worldviews, we need arguments that are understood and endorsed by as much people as possible.[78] As long as some arguments only apply to small parts of our society, a legal framework is never going to address a substantial part of all the existing concerns. Dondorp and De Wert divide human dignity concerning human-animal chimeras into three categories, namely the humanizing of the animal brain, the humanizing of the appearance of the animal and an animal with human sex cells. They do so because they consider this the most morally problematic possible effects of chimerism. For the scope of this essay, and especially for the aim of this essay, an in depth discussion of these points is unnecessary, however what is important is to acknowledge that these three possible outcomes are most likely obstacles for many people, and deserve therefor adequate attention in regulation. If and to what extend we should fear the humanization of animal brains or appearances deserves more time and research, but for now it is sufficient to understand that these things most likely do indeed

[74] Kass, New Republic 1997/216, p. 19
[75] Jochemsem, Dondorp & de Wert 2017, p. 74
[76] Robert, Baylis, The *American Journal of Bioethics* 2003/3, p. 4
[77] Jochemsem, Dondorp & de Wert 2017, p. 77
[78] Jochemsem, Dondorp & de Wert 2017, p. 77

need to be addressed by regulation when further development of chimeras will not become prohibited.

Dondorp and De Wert then address a couple of issues that see on the responsible integration of this technology into society. Again, an in depth discussion upon these subjects is not necessary for the sake of this essay, however again this are subjects that will in time need to be regulated, and are do not entail 'only' ethical points of view. First and foremost, safety regulations will need to be in place. Dondorp and De Wert focus on infections and possible outbreaks, but health and safety regulations should also cover strict rules regarding the living environment of the chimeras.[79] This should of course always be the case regarding research and test animals, and legislation regarding these subjects does already exist. However, this does not mean that a more specific framework might not be more appropriate, and this does also deserve some regulatory attention beforehand.[80]

Interestingly, they also mention the aspect of patient-privacy, as it is highly likely that patients will be monitored for the rest of their lives. Dondorp and De Wert imply that it might be wise to already start to assess possible monitoring systems, as these might have quite an impact on patients' private life.[81]

All the abovementioned arguments can be divided in two categories. On the one hand there are strongly ethical, highly academically arguments and reasoning, often shaping and substantiating concerns that the public has. These concerns need to be addressed in some way. This can either be by discussion or explanation, but this cannot always be sufficiently addressed by regulation. Concepts like human dignity regarding chimera-research might be very hard to form into direct regulation, but nonetheless need to be discussed and understood, because otherwise regulation is never going to sufficiently address a substantial part of the concerns.
On the other hand there are aspects concerning this invention that need regulation, that are not as ethically challenging and not necessarily very specific for chimeras. Health and safety regulation, privacy rules and animal welfare will need tailor-made approaches, that do take into consideration the on-going ethical debate, however they concern more tangible aspects of biotechnological inventions. It is not a very strict boundary, but the one category seems to deal more with the concerns regarding the technology itself and its outcomes – how are we going to frame this technology in a way that concerns are addressed as thorough as possible, whereas the latter focuses on the procedure of the technology – once it is here, how are we going to make sure we are going to use it in a just, safe and respectful way.

4.3 Emerging technologies and the law

As the abovementioned considerations really reflect on the possible ethical dilemmas that should be taken into consideration when drafting a legislative framework for human-animal chimeras, another underlying discussion is also of importance when trying to create a solid legal framework. A broader perspective, that of the considerations that should be taken into account when trying to legislate fast developing technologies. Emerging technologies are often far ahead of the law, and states can find themselves in grey areas, as happens now with human-animal chimeras through induced pluripotent stem cells. There might often not be sufficient time to wholly evaluate all the possible outcomes and possible ethical objections.

In the international legal community the limits of legislation, specifically when it

[79] Jochemsem, Dondorp & de Wert 2017, p.87
[80] Jochemsem, Dondorp & de Wert 2017, p.88
[81] Jochemsem, Dondorp & de Wert 2017, p.88

concerns emerging technologies, have been an important topic. It has been concluded that legislation is often out-dated, and that revision takes too long or is simply not efficient. This is often due the complexness of the technology, the amount of stakeholders involved and the fact that the topics are often highly controversial.[82] While establishing a new legal framework for human-animal chimeras, science will play a big role. Scientists will be major factor in determining if the technology can be deemed safe and will be trying to identify what the risks are. However, it can be argued that the final decisions regard the technology will be with the public. The acceptance of a new technology is a societal choice, rather then a scientific one – science can only lay the foundation for this process.[83] Without undermining the importance of a legal framework for a new technology, it should be kept in mind that legal certainty will always only be certain to a particular degree. Legislation will always be influenced by political decision-making, especially when it concerns a technology like chimeras, which touches upon the boundaries between human and animals.[84]

Chimeras through IPS are one of the many examples of where the legislator had a too narrow scientific foresight. Although these difficulties are neither new nor are at all specific for chimeras, it is important to keep this bigger picture in mind when considering a new or amended legislative framework.

[82] Reins 2017, p. 240
[83] Reins 2017, p. 244
[84] Tallacchini, *Toxicology and Applied Pharmacology* 2005/207, p.645

5. Conclusion

The Embryo Act does not prohibit the creation and further development of human-chimeras through IPSs, as they do not fall under the scope of the article, but it can hardly be deemed regulated. The Special Medical Procedures Act, which prohibits xenotransplantation, was never drafted with this particular situation in mind, but for now prohibits organ transplantation between humans and animals.

The aim of this research was to determine if Dutch law is applicable to human-animal chimeras through IPSs, and if so, they can be relaxed, and if they did not apply it was important to determine if there was a need for more restrictive rules. The answer probably lies somewhere in between. The Special Medical Procedures act applies to organ transplantation between humans and animals, however at the time of the drafting of the provision other health and safety concerns were the basis of this prohibition. It is therefor wise to analyse the possible health hazards of this particular invention and evaluate again is human-animal chimeras through IPSs would fall under the scope of this article. In the case of the Embryo Act, that does specifically mention chimeras, it is not so much regulating the technology, but more accidentally allowing it. It can be argued that this cannot be deemed sufficient in the long run as, based on the Explanatory Memorandum, the underlying considerations do not always directly also apply to human-animal chimeras through IPSs. Further development of the animal embryo, past 14 days, is allowed, thus chimeras can legally be used for toxicity trials and, for example, their (human)organ development can be studied. These are definitely things we can expect to be possible in the near future.

However, it is highly likely that the government is waiting until these uses become more concrete and safe before they start acting, as especially the growing and harvesting of human organs is ground-breaking, but with a lot of difficulties that are not solved yet.

Several ethical considerations have been mentioned, but after reading the Explanatory Memorandum of both the Embryo Act as well as the Special Medical Procedures Act, it seems that the main concern (that is mentioned) is that of public health and public safety. Ethical consideration are often not even mentioned, however, referring to the reports as commissioned by the Ministry, it will always play a substantial role while drafting the legal framework.

As mentioned by Dondorp and De Wert, it is true that if we want to obtain a leading role in the development of this technology, we do need a different and better framework. Not only to obtain a leading role, but also to speed up the research process and make sure the waiting lists for organ transplantation can be shortened as soon as possible.

However on the bright side, it can be argued that even though the Minister is fully aware of the so-called legal loophole, the government has not acted just yet. It might therefor be very well possible that the Government is just awaiting the results of this research and simply feels no need to be in the scientific forefront. This is a safe political choice, as it does not deprive the public from the possible benefits as soon as the technology is fully developed.

Nonetheless, if this would be the point of view of every State, a lot of technologies would never develop past infancy. It might therefor be wise to truly reconsider the possible benefits and the important changes that human-animal chimeras could make. It will take a dedicated, involved international scientific community to make this work, and

governments should fully understand their responsibility, as the legislative framework will be an important factor of the success of this new technology.

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