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FROM THOUGHT TO LABORATORY EXPERIMENT?
GENETIC PAIN DISENHANCEMENT IN THE AGE OF GENOME EDITING: AN ATTEMPT TO ENHANCE THE DEBATE

SAMUEL CAMENZIND
Universität Wien
Institut für Philosophie
samuel.camenzind@univie.ac.at

ABSTRACT
With the advent of genome editing technologies, genetic pain disenhancement (GPD) – the biotechnological reduction or elimination of the sensation of pain in animals as an animal welfare measure – has gained new momentum. Various scientists and philosophers assume that GPD animals can and should soon be used in straining animal experiments or intensive livestock breeding. However, for the current GPD debate to progress from thought experiment to a realistic assessment of GPD, it is necessary to overcome numerous shortcomings and research gaps. This article addresses three research gaps of the current GPD debate and aims to open up new research horizons. First, the central subject of the discussion – (animal) pain – is underdetermined. In many articles on GPD, neither a minimal *definition of pain* is articulated nor are current research findings and questions of *philosophy of pain* and neurobiology considered. Second, at present no or hardly any *empirical data* on animal experiments are included in the ethical analysis. For example, there is a lack of data on the number of GPD test animals currently used, the degree of strains and the state of health of these animals. The inclusion of such data is necessary because the GPD project assumes that all sentient animals have a moral status, including the animals used to develop a final GPD model. Third, the *sociopoliticaldimension* has not yet been sufficiently considered. Whether the population would buy food products from genetically modified, pain-free animals and what the consequences of GPD would be for the field of animal research remain open questions.

KEYWORDS
Genetic Pain Disenhancement, Animal Ethics, Genome Editing

1. INTRODUCTION

Expectations are high regarding genome editing technologies.[1] In addition to the development of more valid animal models, increased efficiency in animal

[1] Genome editing technologies include – among others – zinc-finger nuclease (ZFN), transcriptionactivator-like effector nuclease (TALEN) or clustered regularly interspaced short palindromic repeats (CRISPR/Cas).

farming or other benefits for the human species, the improvement of animal welfare and animal health are also mentioned as objectives and aims of genome editing.[2] These developments also include so-called genetic pain disenhancement (GPD), the biotechnological reduction or elimination of the sensation of pain in animals as an animal welfare measure.

With the introduction of genome editing technologies, the debate about the ethical justifiability of GPD has gained new momentum and various scientists and philosophers assume that GPD animals can and should soon be used in straining animal experiments or intensive livestock breeding (Shriver, 2009; Shriver & McConacchie, 2019; Devolder &Eggel, 2019; Fischer, 2020)[3].

This article focuses on the transition from a thought experiment to GPD as a real possibility in the laboratory. Various shortcomings and research gaps in the current debate around GPD will be addressed and suggestions are made concerning how the debate can be improved if the goal is to achieve a valid ethical evaluation of GPD. Three shortcomings of the current debate will be examined in the first instance. First, the central subject of the discussion – (animal) pain – is underdetermined.In many articles on GPD, neither a minimal definition of pain is articulated nor is GPD placed into the context of current research findings and questions of neurobiology or the philosophy of pain. This represents a serious problem for the debate, because without a minimal definition of pain, it is unclear whether the authors are referring to the same subject. Furthermore, as it will be shown below, it is a complex and open question if and how pain can be modified by genetic engineering.

Second, no or hardly any empirical data on current animal experiments are included in ethical analyses and evaluations. For example, this is a lack of data on the number of GPD research animals currently used, the degree of stress and the state of health of the GPD research animals.

Without robust empirical data, the discussion remains at the stage of a thought experiment. Indeed, exploring GPD as a thought experiment is a legitimate and fruitful philosophical method. However, GPD as a thought experiment should not be promoted as a concrete possibility for action or a realistic proposal for a solution to various ethical problems.[4] The inclusion of empirical data is especially necessary because the GPD project assumes that all sentient animals have a moral status. This means that the pain and suffering of actual laboratory animals is also morally relevant and must be considered. One might argue that the pain of exist-

[2] An overview can be found in De Graef et al. (2019).

[3] Here, it should be mentioned that Shriver's 2009 article was published before current genome editing technologies were developed, although the optimism about biotechnological possibilities was already present.

[4] In fact, GPD has already been discussed in national ethics committees and socio-political debates (Ferrari et al., 2010; Compassion in World Farming Report, 2019) or promoted as a possible solution for welfare problems in xenotransplantation (Bobier et al., 2023).

ing animals is even more relevant than the pain of not-yet-existing animals. This could be a new argumentation line to follow regarding the non-identity problem (see below 2.1).

Third, the socio-political and legal dimension has not yet been sufficiently considered. Whether the population would buy food products from pain-free animals that were cloned or genetically modified is an open question. Particularly in Europe, where GMO foods are viewed critically by a majority (see 5.), it would be possible that GPD animals are only accepted in animal experiments but not in livestock breeding. Given that GPD would have the strongest influence in livestock breeding, this would significantly reduce the performance of GPD.

The question also arises concerning what consequences GPD animals would have for animal research. Since most European countries legally prescribe the "relative replacement principle" and the "refinement principle" – which demands that animals should be used in animal experiments that suffer the least – conventional animal models would have to be replaced by GPD models (at least in the long term). The financial incentive to develop a GPD model is therefore immense. Regarding this point, some speculative thoughts about the possible impact on the field of animal research will be expressed.

This article does not intend to formulate an argument for or against GPD. However, the many unanswered questions urge caution in overestimating the potential of GPD at the present time and they warn against counting on GPD as a quick fix to solve problems that are ultimately attributable to ethically problematic or inadmissible forms of animal instrumentalization. As will become clear, the three topics are too complex to be dealt with in detail in a journal article. However, the article opens new research horizons that need to be explored. In order to address the three topics, (2) the *basic empirical and ethical assumptions* of GPD are explained first, before the three topics concerning (3) the *complexity of pain* and philosophy of pain, (4) the lack of *empirical data* regarding the morally considered GPD research animals and (5) the *socio-political dimension*are discussed individually.

2. ANIMAL DISENHANCEMENT

2.1 Origins and idea

The term "animal disenhancement" was first used by Paul Thompson (2008), and it refers to the alteration of animals to better suit their environment (the laboratory, the stable, etc.) by either natural breeding or via biotechnological reduction or elimination of capabilities in non-human animals to mitigate animal welfare

problems[5]. Genetic pain disenhancement is a specific kind of disenhancement that aims to reduce the animals' experience of negative emotional states such as pain by limiting or erasing their capacity to have those states. The core idea is not new and dates to the first wave of genetic engineering of animals in the 1980s and 1990s (Macer, 1989; Comstock, 1992; Rollin, 1996). However, the advantages of genome editing have fueled hopes that these animals can soon be produced and bred. For the ethical debate, GPD is an interesting case due to several aspects. (i) The genome of a specific animal is modified at a development stage where no living being with a subjective experience of welfare exists. This raises the so-called non-identity problem, which circles around the question of whether you can harm a being with specific breeding traits that would not exist without being bred. This problem will not be discussed here.[6] (ii) Nevertheless the concept of harm is crucial to the debate and the ethical evaluations of GPD.[7] (iii) A third argumentation line coming from the critical theory questions the basic assumption and context of GPD exploiting systems (Ferrari, 2012; 2015). (iv) Regarding the animal model, it ethically makes a difference if pain receptors (nociception) of an actually sentient being are modified, if they are temporally suspended or if the genotype is modified in such a way that the genome modification results in "totally decerebrate animals, animals that experience no conscious life at all" (Thompson, 2008, p. 310).

According to some authors, GPD ideally results in otherwise healthy sentient animals with some kind of experimental welfare. The ontological status of these GPD animals can be described as fully functional "biofacts" (Karafyllis, 2003), as fully functional systems that are capable of auto locomotion, self-maintenance, survival, and reproduction. Whether these animals also function in a social setting remains unanswered (see below 3.). In this inquiry, the focus will be placed on this model. The future debate could be improved here if it were clearly stated to which GPD model the analysis refers, whereby it would be possible for different lines of argument to develop.

2.2 Main premises of GPD

Depending on the context of use, there are different ways in which the argument for GPD is formulated.[8] In abstract terms, the argument can be reduced to two empirical premises (i and iii) and one normative premise (ii), which will be outlined here:

[5]Depending on the ethical theory the term "disenhancement" is not undisputed (Shriver, 2021). For this article this terminological debate can be neglected.

[6] For the discussion of the non-identity problem related to GPD, see: Palmer (2011), Ferrari (2012), Henschke (2012), Murphy &Kabasenche (2018), and Fischer (2020).

[7] A comparison between the sentient and non-sentient harm concepts in the context of different animal welfare laws has been made by Eggel& Camenzind (2020).

[8] For the stable, see Shriver (2009); for the laboratory, see Fischer (2020).

(i) *Non-ideal world premise*: We do not live in an ideal world, and it is highly likely that animals will experience human-induced stress, pain and suffering in the future. These strains affect different contexts of use and include animal experimentation, intensive livestock breeding as well as defective breeding (*Qualzucht*) in the pet sector, as an area that has received insufficient attention in the debate on disenhancement. Transhumanists[9], utilitarians and other philosophical schools who see also the suffering of wildlife animals as a moral problem could also extend the non-ideal premise to non-human-induced strains that occur in nature.

(ii) *Moral status premise*: This normatively crucial premise implies that at least all sentient animals have a moral status. This means that the stress, pain and suffering that they experience are morally relevant. Based on premise (ii), a moral problem arises if the use of animals is associated with strains for the animals.

(iii) *Biotechnological solutionpremise*: Biotechnology and genome editing techniques in particular can be used to modify the genotype of an animal in such a way that the animal phenotype no longer feels pain, or the pain experience is reduced. In contrast to basic or applied research where the genome of the animal is modified for external ends, based on premise (ii), the genome editing is undertaken for the animal's sake. The ideal GPD animal model would still be sentient and able to experience positive states of consciousness, but the ability to experience pain would be reduced or eliminated.

3. COMPLEXITY OF PAIN AND PHILOSOPHY OF PAIN

Ronald Melzack – one of the central figures of pain research of the last century and co-founder of the Gate Control Theory – stated: "Because every aspect of pain is the subject of vigorous debate, it is impossible to discuss pain without taking a theoretical point of view." (Melzack, 1973, p. 11). Unfortunately, a confrontation and dispute about the complexity of pain or current research of neurobiology, the philosophy of pain and philosophy of mind has not been given sufficient consideration in the GPD debate[10]. The opinions and arguments from philosophers, neurophysiologists, and biologists about pain as a general phenomenon range from the position that pain is completely objective (intrinsic to a body part, functional state, set of behavioral reactions or perception) to it being considered

[9] For transhumanists who strive for a pain-free world for all sentient beings, GPD may only represent the first step in a long-term project (Pearce & Vinding, 2017/2018).

[10] An overview of the current state of research can be found in Bain et al. (2019) and Corns (2020).

completely subjective (private mental state) or totally mysterious[11]. Besides the issue that the complexity of pain is not addressed at all, the problem of classifying pain theories in the GPD debate is compounded by the fact that in many articles even a minimal working definition of pain as the subject of investigation is missing (Hongladarom, 2012; Henschke, 2012; de Graeff, 2019; Fischer, 2020)[12].

Such a definition is articulated by the International Association for the Study of Pain (IASP), which describes pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (International Association for the Study of Pain, 2011). Although this definition has been under critique (Fink, 2012, pp. 4ff) for being too narrow and not applicable to cases of pain asymbolia, it serves as a useful starting point to discuss which kind of types of pain are covered by GPD.

Types of pain are systematically ordered by spatial or temporal distinction. Spatial types include *somatic pain* (fracture pain, superficial burn pain, muscle pain), *visceral pain* (stomachache pain, labor pain, bladder pain) and *neuropathic pain* (central pain, peripheral pain), while temporal types consist *acute* and *chronic pain*.

Based on this distinction, it should be clarified whether GPD focuses on all of these types of pain, only a few of them or only a single type. Alternatively, does GPD even go further and aim to reduce or eliminate other negative experienced states such as distress, hunger thirst, itching, anxiety, boredom or loneliness? This question is relevant because all of these states occur in the laboratory, the stable, the private living domain or the zoo. Such differentiations regarding pain types are not yet present in the GPD debate. But they are important to assess the performance of GPD.

The IASP definition also includes the distinction between sensory and emotional aspects of pain, which is relevant for the current GPD debate and the envisaged GPD animal model. In the current debate, a specific understanding of pain – I will call this view the "dual theory of pain" – is dominant, it has been introduced by Adam Shriver (Shriver, 2009; Devolder &Eggel, 2019; Camenzind &Eggel, 2022). The dual theory of pain is based on the distinction between the *sensory* and *affective dimension* on pain, which are said to have different neural correlates.

The affective pain dimension is connected with the *anterior cingulate cortex* and the *primary* and *secondary somatosensory cortices* with the discriminative dimension. In other words, while the *primary* and *secondary somatosensory cortices* are associated with processing sensory properties such as pain location, intensity and quality, processes in these areas are not sufficient conditions for experiencing sensory properties as unpleasant. Interfering with these pathways could potentially reduce or eliminate the experience of normally negative sensory input while

[11] For an overview of different positions, see Hardcastle (1999, p. 95).

[12] Ferrari has already identified the problem about sentience (Ferrari, 2008, p. 181).

leaving the acute pain response (e.g. muscle reflex) intact, although this is counter-intuitive for the average experience of pain of human animals, which experience pain holistically. A simple pain experience includes – for example – noxious stimuli (heat, pressure or a chemical stimuli), the transition of these stimuli via nerve paths to the brain ("pain" sensation),[13] where it is assessed as negative (pain affection), followed by the initiation of a physical action, such as moving the hand or scratching it.

Now, patients with a corrupted pathway (sensory-limbic disconnection syndrome) between the two dimensions can make statements such as "Oh, yes, it [the pain, S.C.]'s still there. I just don't worry about it anymore" (Grahek, 2012, p. 32). In this case, the "pain" sensation is still working, but the evaluation of the sensation is different. In contrast to early thought experiments on painless animals, which are based on the animal model called "animal microencephalic lumps" (AMLs; largely brainless, motionless and fully insentient living beings), GPD animals are otherwise healthy sentient and therefore conscious animals with some kind of experiential welfare. In other words, it is assumed that stimuli sensation and physical reactions (e.g. reflexes) will work regularly but the GPD animals will not experience them as negative.

Although the distinction between the sensory and affective pain dimensions and their neural correlates in the brain does more justice to the complexity of the phenomena pain than previous understandings – for example – the view that pain is processed in some sort of a (single) pain center, the question remains whether it is sufficiently appropriate.

The dual pain theory locates the badness and unpleasantness of all pain types (and even other negative experienced mental states) in a specific brain area. If this affective part of pain can be modified or disconnected from the sensory part, then the central problem of pain – the painfulness of pain – is solved.

However, the dual pain theory is just one of several competing theories (Allen, 2004, p. 620). For example, Robert Coghill argues that the dual pain theory fails to account a number of aspects of pain (Coghill, 1999, p. 67). The reason for this is that – as he concludes – "[...] although individual brain regions and networks of brain regions exhibit some degree of functional specialization, pain is clearly processed by a highly distributed brain system" (Coghill, 1999, p. 73). It is necessary to further examine how this critique affects GPD in particular.

Another competing theory regarding the different type of pains is the Family Resemblance Theory of Pain,recently developed bySabrina Coninx. She argues that "[t]here is no single property or set of properties that accounts for the commonality of all pains as well as of the specificity of pains in comparison to other

[13]"Pain sensation" is the common term used in the literature. I put "pain" in quotation marks because without the affective dimension and negative evaluation, the stimuli sensation is not yet pain.

mental phenomena" (Coninx, 2020, p. 161). What would this view on pain would mean for GPD? This is not the place to decide which of these pain theories is the most accurate, but simply the fact that several competing theories exist and should be regarded in any GPD project.

Moreover, if biotechnology and genome editing should be the methods to modify or eliminate the pain experience, then the relation between genetics and the pain experience must be regarded. Accordingly, it might be possible that the pain experience for specific forms of pain can be modulated by using genome editing, although the fact that at least 358 genes (Mogil, 2012, p. 259) are thought to be relevant to pain or analgesia urges caution that modifying the genome will be an easy task. The idea that the pain experience can be easily "switched off"is likely to be inaccurate. The modification of the genome to influence the pain experience rather seems to be a complex undertaking.

Another problem that is related to the complexity and neurological structures of pain concerns the premise that the GPD animals will be healthy and otherwise fully functioning animals.[14] Any of the aforementioned pain theories will face the problem that depending on the context:

> [i]t became also clear that most of the activated areas were not specific for pain: PM (pain matrix; S.C.) regions such as the anterior cingulate cortex, the anterior insula, and the prefrontal and posterior parietal areas showed enhanced activity in a wide range of non-pain experiments, especially in emotionally or cognitively laden contexts, whereas the sensory encoding of noxious intensity was reflected by very tiny brain activations. (Garcia-Larrea & Peyron, 2013, pp. 29f)

If this is true, then it remains an open question how pain elimination will affect the whole organism.

4. EMPIRICAL DATA AND MORAL CONSIDERATION OF GENOME EDITED RESEARCH ANIMALS

The (ii) *moral status premise* states that all sentient animals have a moral status. This means that possible strains, pain and suffering of the animals that are used to develop GPD animal models of so-called first-generation progenies (generation F 0) are morally relevant. Therefore, the ethically relevant question emerges concerning whether strains, pain and suffering occur during the process of modifying the genome via genome editing.

It has already been stated – albeit without referring to genome editing – that "the lack of a precise reference to empirical facts related to genetic engineering

[14]Thinking of pain in form of a matrix supports this point of critique, which hasalready been mentioned (Macer, 1989, p. 231; Ferrari, 2012, p. 70; Eggel& Camenzind, 2020, p. 3).

methods affects the ethical evaluation" (Ferrari, 2012, p. 68). Based on announcements dating back fifteen years that GPD animals will soon be available, one might expect that the debate refers to precise empirical data on ethically relevant parameters in the meanwhile. Among others, these include the number of research animals used, the existing strains for the animals and possible unintended side effects. If the GPD debate wants to progress from the stage of a thought experiment, then empirical data must ultimately be included.

Regarding animal welfare, this problem will be discussed in detail below. Based on data from other biotechnological applications such as xenotransplantation, serious moral issues must be expected.

These moral issues concern the concepts of sentient harm and non-sentient harm. Sentient harms are defined as subjectively experienced negative welfare states (so-called "subjective harms") such as pain, distress, and fear. These forms of harm are predominant in transhumanism and utilitarianism, which both mainly promote GPD, and these harms are also most frequently referred to in the debate. But as others have already pointed out (e.g., Ferrari 2012, Eggel& Camenzind 2022, and Perez et al. 2024), in addition to sentient harms, non-sentientist harms should not be overlooked in the assessment of GPD. Non-sentientist harms include those that do not necessarily cause or involve negative subjective experiences for the affected individual, such as altering an animal's species-specific appearance or abilities, which are also referred to as "objective harms".

Especially in the context of genetic engineering, non-sentient harms should be considered, as thirty years ago, classical genetic engineering triggered a significant paradigm shift in the ethics of biotechnology. This shift not only affected areas such as the moral consideration of animals, but also spurred the development of new concepts like animal integrity (Rutgers & Heeger, 1999), telos (Rollin, 1996), and animal dignity (Balzer, P., Rippe, K. P., & Schaber, P., 2000). These concepts all addressed non-sentient harms to capture the moral intuition that harm should be understood more broadly than just in subjective terms.

4.1 Welfare risks for genome edited research animals

The problem of missing empirical data that is relevant for an ethical analysis is not only present in the disenhancement debate but also concerns animal biotechnology areas such as xenotransplantation (Camenzind, 2023, p. 34). In contrast to SCNT cloning (see below), where species-specific data was available about animal welfare and potential risks within a few years after the birth of Dolly the sheep – the first SCNT-cloned mammal – after a decade this situation is still not the case with genome editing:

> While this method [CRISPR/Cas9; S.C.] is generally considered to be much more efficient and specific compared to other approaches, any accurate, definitive, quantitative estimation of the efficiency of CRISPR is difficult to find, as estimates vary considerably and are affected by many factors, including the nature of the target site and the CRISPR molecule used. (Bailey, 2019, p. 446)

What are current safety problems with genome editing and what kind of parameters would be necessary for an ethically sufficient evaluation? An informative evaluation of genome editing should include on-target efficiency, non-intended on-target effects and non-intended off-target effects.

The *on-target efficiency* provides information on whether the desired modification has been successful at a specific location in the genome. The non-intended on-target effects refer to unintended changes and effects near the target. Therefore, despite the fact that CRISPR/Cas allows precise changes in the genome, it is possible that in the target-sequence unintended DNA fragments are inserted, deleted or the function of a gene is reduced or deleted (Kawall, et al., 2020; Weisheit et al., 2020;European Network of Scientists for Social and Environmental Responsibility & Critical Scientists Switzerland, 2021, pp. 28f). Under the bottom line, the on-target efficiency ranges between 2% and 100%, and it can vary depending on the species, cells, and modifications (knock-in, knock-out, knowdown) (Withworth et al., 2016; Fischer, 2017).

Further off-target effects can be expected. These are non-intended gene modifications that can also occur far away from the target sequence (Kosicki et al., 2018). In order to recognize them, the whole genome of the organism has to be decoded, and a comprehensive test method that covers all off-target effects does not yet exist. While in some CRISPR experiments over 100 off-target mutations were detected, in others none of them were found (Bolukbasi et al., 2016). Although off-target effects do not necessarily negatively affect the phenotype, from a risk ethics perspective it is important to state that a single non-intended genetic modification may negatively affect the welfare of animals or lead to lethal anomalies (Bailey, 2019; Solomon, 2020; European Group on Ethics in Science and New Technologies, 2021, p. 51). Whether and which risks are ethically relevant, and to what extent, depends on the ethical position. But, in sum, for humans and for other animals, "current genome editing technology does not have sufficient efficiency and specificity to be reliably safe" (Carroll, 2017, p. 655).

4.2 Genome editing and SCNT cloning

As mentioned above, because it is difficult to achieve any accurate estimation of the efficiency and risks of CRISPR, a definite ethical analysis and evaluation is not possible. Interestingly, despite the advantages of the new genome editing technologies, they do not simply replace earlier biotechnologies but rather are combined

with them. A closer look at the recent developments and milestones in xenotransplantation reveals that SCNT cloning is prominently present (Camenzind, 2023, p. 52). SCNT cloning was involved in the first successful experiments with TALEN, ZFN and CRISPR as well as in the multiple genome edited pigs, which were used for the first clinical trials in 2022 (Singh et al., 2022).

Why is this relevant for GPD? Although it is possible to use genome editing technology without SCNT, it is highly likely that SCNT cloning will also be used in GPD research. In the context of gene technology, SCNT cloning can fulfill two functions: it can be used to either produce genetically modified animals or maintain a line of genetically modified animals, if the genetic modification cannot be stably integrated in the genome of the animals.

Because SCNT cloning allows pre-selection and screening of the genome, it remains a common technique for producing genetically modified animals in combination with TALEN, ZFN and CRISPR/Cas (Kurome et al., 2015; Tan et al., 2016; Fischer &Schnieke, 2021). However, the crux with SCNT cloning is that in general it remains a challenging technique that is still unsecure and inefficient (Cowan &Tector, 2017, p. 2531; Nuffield Council on Bioethics, 2021, p. 17). If genome editing technology is combined with SCNT cloning, this can have an additional negative impact on animal welfare (de Graeff et al., 2019, p. 651). The live birth rate (LBR: live born animals per transferred embryos) of mice – for example – which are the most widely used research subjects, ranges between 0.5% and 16%. In cattles, the LBR can increase to 87% (Camenzind, 2011; Schreiner, 2015). However, 30–40% of the clones born alive suffer from health-related strains, which can be lethal. Among them are diarrhea, meningitis, cardiopulmonary functional abnormalities and cerebromeningitis, malformations, asphyxie through *respiratory distress syndrome*,or in pigs *adult clone sudden death syndrome* is known (Park, 2005; Schreiner, 2015). If the offspring of the clones are born through conventional breeding techniques, neither of these strains appear (European Food Safety Authority, 2012, p. 13).

To sum up, it can be expected that the SCNT cloning of GPD animals result in abortions at different stages of birth, deformities, and weak young animals. The health and welfare risks for the animals involved in SCNT cloning range from no strains to mild, short-term stress (e.g. cell nucleus harvesting from live animals, oocyte harvesting from anesthetized animals, planned cesarean section for the surrogate mother) and moderate strain (e.g. embryo transfer to the surrogate mother, unplanned cesarean section) to severe strain (lung failure or heart insufficiency of the clone) (Camenzind, 2011, p. 46).

How these welfare risks are to be evaluated depends on the ethical theory (welfarism, Utilitarianism, Kantianism, ect.) that will be applied. Nonetheless, because

the subjective welfare of animals is relevant in every ethical theory[15], where animals have a moral status, it is necessary to consider these welfare risks.

5. SOCIO-POLITICAL CONSIDERATIONS

Despite social movements of veganism, vegetarianism or flexitarianism, global statistics about meat production definitely confirm the (i) *non-ideal world premise*, that people will continue to eat meat. Indeed, trends even show that meat production is still growing (Heinrich Böll Stiftung, 2021). Another empirical premise in a potential argument pro GPD livestock is that "[p]eople would be willing to eat genetically engineered food if it meant they were no longer responsible for suffering and if it did not impose too much of a burden on their lives" (Shriver, 2009, p. 119). However, crucial to this premise is the question whether people would also eat meat and dairy products from pain-free animals that are cloned or genetically modified.[16]

Future research should focus on this question with empirical studies from the social sciences. The premise of what kind of meat people are willing to eat is important for the impact of GPD in livestock farming and a positive answer should not be taken for granted for at least two reasons. First of all, not all consumers who prefer to eat meat are in favor of products from cloned or genetically modified animals. For example, a significant number of Europeans (58%) are very skeptical about animal cloning for food production and consider it unlikely that they would buy meat or milk from cloned animals (European Commission, 2008). The Enviropig is another study case, as a transgenic pig developed by researchers at the University of Guelph in Ontaria. The genetically modified pig excreted less phosphorous in its feces, being breed for environmental reasons. In North America, the transgenic pigs were not well received and after losing the main funding source the pigs were killed (Clark, 2015). Project leader Cecil W. Forsberg was incorrect when he estimated that the Enviropig would be accepted by the public in 7–8 years. Regarding the ethical costs required to create a GPD animal and prevent them from ultimately being used, empirical studies are necessary to estimate the impact of GPD animals in the context of the livestock market.

Another path that has not yet been mentioned in the context of the laboratory but is worth tracing is the consequences that GPD would have for the field of animal research. If GPD animals would actually exist and carry a stable genetic mod-

[15] An overview how animal welfare is considered within different positions in animal ethics can be found in Schmidt (2011).

[16] Shriver recognises this issue and refutes different arguments contra GMO food (2009, pp. 122–123). But this strategy doesn't meet my critique, because it concerns, what people really do and not what they should ideally or rationally do. Otherwise,one couldgive sufficient ecological, health-related and moral reasons, why people should eat less meat or restrain from eating meat completely. In this case the argument pro GPD is be attacked already in the *non-ideal world premise* (i).

ification that prevented them from the pain experience, at the present time this scenario would lead to a major practical disruption in animal research, at least in Europe. In the European Union and other countries such as Switzerland or the United Kingdom, it is a legal requirement to choose the animal species that is least sensitive to pain for an animal experiment[17]. These countries have implemented the 3R principles from William Russel and Rex Burch in *The Principles of Humane Experimental Technique* (1959) by law. The principles state that an animal experiment is only permissible if there is no alternative to answering the research question (Replace) that the number of animals should be kept as low as possible (Reduce) and that the animals should be subjected to the least possible stress (Refine). Regarding the fact that GPD would affect more than 6,878,000 animals annually in the European Union taking rodents alone into account (European Commission, 2020), the economic potential of GPD is enormous.

Regarding the economic effects, different scenarios are possible to imagine. If one biotechnological company will be able to breed GPD animals and secure a patent, they will have a monopoly, and the animal research sector will be dependent on their terms. Another scenario is that several companies will try to develop different strains of GPD animals, and perhaps even strains of different GPD models. According to current data about the efficiency of SCNT cloning and genome editing, this will lead to an unimaginable amount of animal research. This would fit into the picture that historically biotechnological developments in the context of animal testing and genetic engineering have led to an increase in the number of animal experiments to date (Ferrari, 2006).

6. CONCLUSION AND RECOMMENDATIONS

While exploring GPD as a thought experiment is a legitimate and fruitful philosophical method, if the debate wants to progress and focus on GPD as a realistic solution for welfare problems of instrumentalized animals in the context of animal research, livestock breeding and eventually companion animals, the following recommendations can be made:

– The debate on animal disenhancement can be improved if authors provide a definition of what *kind of pain* and what kind of *GPD animal model* they are referring to. Given that the different models are related to different ethical questions, this may lead to different argumentations lines within the GPD debate. From a theoretic-scientific, ethical and practical view, a more differentiated debate is desirable.

[17]Forthe European Union, see European Directive 2010/63/EU (Recital 13); forSwitzerland, seethe Swiss Animal Welfare Act, Art. 20, Par. 1; and similarlyforthe UK, seetheUK's National CentrefortheReplacement, Refinement, and Reductionof Animals in Research (NC3R) (2021).

– Empirical data should be obtained on the number of GPD test animals used, the degree of *strains*, the impact on the pain experience and the state of *health of these animals*. This data is relevant to draw a valid picture concerning the positive and negative impact of GPD, what future GPD animals would gain and what price existing animals would have to pay. Without this data, a realistic ethical analysis and examination is not possible and GPD should not be promoted as an ethical solution for animal welfare problems.

– Further empirical data should be gained about *consumers' attitudes* towards products from pain-free animals that stem from cloned and or genetically modified animals. Depending on the result, the impact of GPD in solving animal welfare problems can be affected.

– Another relevant question regarding the socio-economic dimension is how the field of animal research could change if GPD animals were brought into the market.

No ethical position was taken in this article. This is because the three mentioned research gaps (missing pain definition, missing empirical data on GPD models, and socio-political impact) are relevant regardless of the ethical position that is taken. With filling these research gaps, the GPD debate would gain substance, and more realistic assessments could be made.

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