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# The 3Rs principles and genetic pain disenhancement

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## Abstract

*William Russell and Rex Burch's 3Rs principles were developed 1959 before animal ethics emerged as a scientific discipline in the 1970s and before many ground-breaking developments in modern biotechnology, such as genetic engineering. From this starting point we sought to analyse the normative foundations of the 3Rs principles in contemporary terms and concepts of animal ethics. After establishing the normative groundwork of the 3Rs, we will look at their practical implications within the context of present-day biotechnology. To this end, we shall investigate whether the genetic disenhancement of research animals to limit their ability to feel pain (GPD) complies with the original 3Rs principles. We use GPD as a practical example, since it is being discussed today as a promising way of solving one of the key moral issues raised by animal research, notably animal pain and suffering. By discussing GPD in the context of the 3Rs we aim also not only to gain insights into whether GPD is compatible with one or more of the 3Rs, but also to develop a better understanding of the specific normative foundation of the 3Rs principles and the conceptual limitations and practical implications of that foundation. We argue that reducing moral concerns about animal research to those that are intelligible within a sentientist framework (eg harm and suffering), as the 3Rs do, represents an over-simplification of the moral issues involved. We suggest that interference with abilities, instrumentalisation, flourishing, and death are all important aspects of animal ethics requiring consideration.*

**Keywords**: *animal ethics, animal research ethics, animal welfare, genetic engineering, genetic pain disenhancement, 3Rs principles*

## Introduction

The 3Rs principles — Replacement, Refinement and Reduction — were set out by the British scientists, William Russell and Rex Burch in 1959 in *The Principles of Humane Experimental Technique*. They were introduced as a measure of professional self-regulation in response to the increasing amount of animal research taking place and the invalid results that were related to inhuman treatment of animals (cf Russell & Burch 1959; pp 3f). Since the 1980s the principles have become an integral part of various legal regulations. They also appear in the official statements of good practice of most European and many non-European universities and research institutions dealing with animal experimentation (Bayne *et al* 2015), as well as playing a crucial role in the ethical evaluation and authorisation of animal experiments in several countries.

The fact that the 3Rs have been successfully implemented across a range of legislative domains based on different ethical theories (themselves based on different moral traditions and schools) indicates their compatibility with a wide range of ethical stances.

However, what is the original meaning, or content, of the 3Rs? Furthermore, what is their normative groundwork? These questions are important for two reasons. First, the 3Rs were developed prior to the emergence of animal ethics as a scientific discipline in the 1970s (Grimm *et al* 2016) and before many ground-breaking developments in modern biotechnology, such as somatic cell nuclear transfer cloning and genetic engineering. Second, notwithstanding more than fifty years of developments in the content and methodology of animal ethics, we claim that ethical evaluation of the presuppositions informing the 3Rs principles and the changing ethical context continues to lag behind scientific and practical efforts to implement the 3Rs (see also Vorstenbosch 2005).

In this paper we therefore aim to analyse the normative foundations of the 3Rs principles in contemporary terms and concepts, and to explain their relevance for contemporary animal research. After establishing the normative groundwork of the 3Rs, we will look at the practical implications of this groundwork. To this end, we shall investigate, from the normative perspective of the original 3Rs, whether the genetic disenhancement of research

animals to limit their ability to feel pain and suffer (hereafter 'GPD' for genetic pain disenhancement) would comply with the 3Rs principles. We use GPD as a practical example, since it is being discussed today as a promising way of solving one of the key moral issues raised by animal research, ie animal pain and suffering. By discussing GPD within the context of the 3Rs we aim not only to gain an insight into whether GPD is compatible with one or more of the 3Rs, but to also develop a better understanding of the specific normative foundation of the 3Rs principles and the conceptual limitations and practical implications of that foundation.

Lastly, from a contemporary standpoint, we reflect critically on the normative position of the 3Rs principles and their underlying concept of harm. We argue that reducing moral concerns about animal research to those that are intelligible within a sentientist framework (eg harm and suffering), as the 3Rs do, represents an oversimplification of the moral issues involved. We suggest that interference with abilities, instrumentalisation, flourishing, and death are all important aspects of animal ethics requiring consideration — and all the more so in light of the possibilities offered by modern genetic biotechnologies, including GPD.

## Overview of the 3Rs principles

The UK's National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3R) distinguishes two forms of *Replacement*. 'Full Replacement' ('absolute Replacement' by Russell and Burch) aims at avoiding "the use of any research animals. It includes the use of human volunteers, tissues and cells, mathematical and computer models, and established cell lines" (NC3R 2021). 'Partial Replacement' includes "the use of some animals that, based on current scientific thinking, are not considered capable of experiencing suffering", eg *Drosophila*, nematode worms and embryonic and fetal forms of vertebrates. Also included here are the use of primary cells (and tissues) taken from animals killed solely for this purpose. Others understand the use of animals that are alleged to be less sentient as 'relative Replacement' (Olsson *et al* 2012).

*Reduction* aims to reduce the number of animals used for a specific experiment to the minimum required to guarantee sufficient statistical power. It also includes methods to maximise knowledge gain per animal used (eg longitudinal imaging). The rationale for this principle is that using either too many or too few animals in a research project is morally problematic. Using too many animals is wrong because no additional knowledge is gained while using too few is problematic because it may jeopardise the validity of a study.

*Refinement* aims to minimise the amount of harm and suffering inflicted on research animals to the scientifically necessary minimum. This not only entails minimisation of negative impacts such as pain and suffering but also includes promotion of the positive well-being of animals (eg through environmental enrichment).

## The normative groundwork of the 3Rs principles

Unfortunately, Russell and Burch do not consider the groundwork of the moral theory their principles are based on in detail, nor do they attempt to justify these principles. For various reasons, this is unsurprising. For one thing, Russell and Burch were not ethicists. They had a background in zoology, psychology and microbiology. They developed a normative framework to assess animal research from within the field of animal research (Vorstenbosch 2005; Grimm 2013). This internal approach may have helped the 3Rs to become a success. The 3Rs principles were not experienced as an external interference restricting scientific freedoms. Instead, they appeared to be a measure of professional self-regulation and a necessary means to progress and develop scientific fields involving laboratory animal use.

From a historical perspective, the lack of moral theory is also not very surprising, given that animal ethics as an academic discipline evolved ten years after publication of *The Principles of Humane Experimental Technique*.

Nevertheless, an outline and justification of the moral framework underpinning the 3Rs would have been valuable. First, as we will try to show, the 3Rs principles represent a unique moral position in comparison with the other ethical approaches being explored in the middle of the twentieth century. Second, such an outline and justification might have precluded different interpretations of the 3Rs and their long-term purpose. For example, it would arguably have been clearer whether the 3Rs are a method to minimise the distress of animals within an anthropocentric scientific framework or instead an abolitionist tool to refrain from animal research entirely (as a final goal). Third, a moral groundwork would have provided normative guidelines allowing us to assess the compatibility of particular practices (such as GPD) with the 3Rs.

Although Russell and Burch do not themselves examine the groundwork of the moral theory their principles are based on, the moral theory they implicitly relied upon can be deduced to a degree. This theory can be described as one that is hierarchical and sentientist. It involves deontological principles.

The first two chapters of *The Principles of Humane Experimental Technique* explain that the 3Rs are based on the ethical principle of humanity. This principle can be articulated in the form of an imperative: 'Treat animals as humanely as possible.' 'Humanely' here is not to be understood in the sense of social co-operation, but rather in the sense of humanness. The notion of humane treatment is explained with reference to subjectively negative experienced mental states such as pain and fear, and distress more generally (Russell & Burch 1959; p 14, 15). Noticeably, and in contrast with later discussions (Russell 2005), the main focus in the 1959 book was not on animal welfare as a phenomenon including both positive and negative mental states. It was on the negative welfare states of pain, fear and distress (Ferrari 2008; p 267). (This will become relevant when we turn to GPD specifically).



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The second chapter of *The Principles of Humane Experimental Technique* also presents a discussion of the nature of the pain that animals are able to experience and asks how distress can be measured. The overall aim of the authors is to examine the "concept of humanity (or inhumanity) as an objective assessment of the effects of any procedure on the animal subject" (Russell & Burch 1959; p 14). The concept of inhumanity is further distinguished into two forms: *direct* and *contingent* inhumanity. The former concerns "the infliction of distress as an unavoidable consequence of the procedure employed", the latter includes "the infliction of distress as an incidental and inadvertent by-product of the use of the procedure, which is not necessary for its success" (Russell & Burch 1959; p 54). Imperfect husbandry conditions and harsh handling would count as indirect in this sense, as would unanticipated post-operative complications and sub-optimal hygiene conditions.

Although Russell and Burch mention death, and the killing and euthanasia of animals in several places, the topic is not discussed extensively from a moral perspective. What is also missing in the first two chapters, and indeed throughout the rest of the book, is a comprehensive consideration and justification of the grounds on which we should treat animals as humanely as possible. Why should we do this? Should we treat animals humanely for their own sake or for other reasons, such as economic or scientific reasons? Or should we show a 'friendly and constructive attitude to the lower animals' because cruelty to animals tends to make the perpetrator callous (Russell & Burch 1959; p 14), a view that is associated with Kant, whose work anticipates the 3Rs principles (Camenzind 2020; p 62f). Both interpretations are possible: Russell and Burch open their survey with a confident assertion that society owes "many if not most of the benefits of modern medicine and countless advances in fundamental scientific knowledge" to animal experimentation, and with the further statement that good animal welfare promotes successful science (Russell & Burch 1959; p 3f).

While the first, historical comment on the contribution of animal experimentation to medical progress has been challenged by medical historians (LaFollette & Shanks 1996), the second claim, that "good quality science depends upon good animal welfare", is still widely accepted today (World Organisation of Animal Health [OiE] 2010; chapter 7.8). In effect, the second claim represents the major theme of Russell and Burch's book. From this claim, we might be tempted to infer that animal welfare has only an instrumental value for qualitatively better, more efficient science. Such an inference would signal a moral anthropocentrism in which animals lack moral status and in which animal welfare is considered, at most, indirectly.

However, it seems unlikely that this was Russell and Burch's intended meaning. This is indicated by the prominent role given in the book to Charles Darwin. Each chapter is introduced with a quote from Darwin, and in the final paragraph of the foreword Darwin is presented as a scientist who was very concerned about the welfare of experimental animals and more active in "furthering the progress of humane experimental technique" than most other scientists (Russell & Burch 1959; p xiv). In addition, the claims the authors make about relative and partial Replacement (see below), and their focus on sentient animals — all vertebrates (Russell & Burch 1959; p 6) — are indicators that Russell and Burch assume the moral status of all sentient animals. So, treating animals in the most humane way, besides being good scientific practice, instrumentally speaking, may also be of direct, moral value. This is a good reason for thinking that Russell and Burch were not working in an anthropocentric paradigm: they were promoting a sentient position that grants all sentient animals moral status (see also Vorstenbosch 2005; Ferrari 2008).

Even if this interpretation is correct, there are a number of reasons to think that the moral significance attributed to animals by Russell and Burch was not very high. First of all, it is obvious that Russell and Burch accept the lexical priority of human interests over animal interests (Rippe 2009; p 6). The infliction of harm such as pain, or suffering, or stress on animals is generally permitted for scientific purposes as long as it is done in a 'humane' manner. The authors do not appear, then, to see animal research as a severe moral problem, or a moral dilemma. Secondly, no harm-benefit-analysis is recommended by Russell and Burch. This means the animal's interest in avoiding suffering (harm scale) cannot outweigh the scientific benefits (benefit scale). In other words, using the 3Rs principles alone results in the position that any scientific goal — even trivial ones — trumps severe harms inflicted on animals.

To conclude, the 3Rs approach essentially aims to promote animal welfare while at the same time striving for scientific validity. Importantly, however, when these two goals conflict with each other, or at least appear to do so, priority is given to scientific validity. We refer to this position as "hierarchical sentientism" or "human priority position" (see also Broady 1998; p 16).

Despite the marginal consideration they give to the animal's own interests, one has to acknowledge the strict bindingness of the 3Rs principles. The 3Rs are categorical duties — they are neither supererogatory ideals nor *prima facie* duties that can be balanced against other moral requirements. Certainly, Replacement and Reduction seem to be perfect (negative) duties leaving little if any room for discussion of how they are to be complied with, although Refinement leaves more room here, allowing us to ask how the distress of animals is best avoided or minimised, and how the positive welfare of animals is to be promoted.

Given the theories, or moral attitudes, that were common currency when Russell and Burch were writing, we can see that their ethical position, in setting out the 3Rs approach, was somewhat new and unique, and far from self-explanatory. Firstly, they departed from the historically dominant anthropocentric paradigm, which excludes animals from the moral community completely. Giving animals moral status, however, they followed the paths of neither Leonard Nelson's (1923) interest-based ethics, which considered animal and human interests to be equal, nor Henry Salt's (1892; p 1)

animal rights account, which claimed, famously, that animals have rights if humans do. Moreover, as mentioned above, against the dominant utilitarian tradition in Great Britain (eg Bentham 1789), the 3Rs principles do not allow us to conduct a harm-benefit analysis. Finally, in contrast with Albert Schweitzer (1923), who expanded the moral community in his ethics of 'reverence for life' to all living beings, including non-vertebrates and plants, Russell and Burch focus only on sentient animals. We can summarise this by saying that the 3Rs represent a hierarchical, sentientist position associated with deontological, categorical, absolute principles to promote the humane treatment of animals.

Having provided some insight into the normative foundation of the 3Rs principles, we will now examine a biotechnological innovation that is currently being discussed as a promising 3Rs method. This is genetic engineering to reduce animals' ability to feel pain and suffer. We wish to discuss animal disenhancement of this kind for two reasons. On one hand, we want to assess whether, and if so how, it complies with the principles of Replacement, Reduction and Refinement. On the other, we believe the assessment will throw light on the ethical foundations of the 3Rs principles, their conceptual focus, and also their limitations, as well as their practical implications for modern biotechnology and animal research.

## Animal disenhancement

Animal research causes pain and suffering to millions of sentient research animals every year (Knight 2019). There is a wide consensus among the general public, politicians, scientists and ethical theorists that this is morally problematic.

The consensus on the moral relevance of animal pain and suffering, and on the desirability of avoiding unnecessary pain, is evident in ongoing efforts to improve implementation of the 3Rs in practice — eg by reducing the suffering of laboratory animals by providing better housing conditions and better pain treatment (eg analgesia and anaesthesia), and through developments in surgical technique, science education and training, and so on. Notwithstanding these efforts to minimise pain and stress, scientific research continues to inflict significant suffering on laboratory animals. This is partly because the opportunities to reduce animal suffering are limited for economic and practical reasons. For example, methods designed to better satisfy the 3Rs will only be implemented if they are affordable, do not impair scientific validity and can feasibly be applied to a large number of individual animals. It is also because pain, suffering, distress and anxiety, in different grades of severity, are integral accompaniments to animal research procedures. As a result of these inherent practical and economic limitations, recent discussion of how we can improve animal welfare further, in practice, has turned to genetic options, including genetic disenhancement.

The term 'animal disenhancement' was first coined by Paul Thompson to refer to the alteration of animals to better suit their environment, either by breeding or via "biotechnological reduction or elimination of capabilities in non-human animals to mitigate animal welfare problems" (Thompson 2008). The idea of altering research and farm animals for specific human use emerged in the course of the 1980s and 1990s (eg Macer 1989; Comstock 1992, 2000; Rollin 1986, 1996; Ryder 1995; Sandøe *et al* 1996). The basic idea is to adapt the phenotype of an animal so that it is better suited to life in the (otherwise harmful) conditions involved in a specific use, such as animal experimentation or livestock farming, through breeding or genetic engineering.

To explain the rationale behind animal disenhancement we need to refer to three historical developments. First, consider the historico-cultural use of animals for human purposes. The intensive use of animals in agriculture and scientific research involves harms to the animals some of which are intrinsic to the procedures and housing systems while others are only contingent side-effects. As a strongly institutionalised practice, animal research that involves stress for the animals is highly likely to continue in the future. This fact becomes morally relevant in view of the second historical development.

Second, the emergence of animal ethics and the rising moral status of animals in academia and society over the last fifty years have significantly altered our understanding of the human-animal relationship. For example, the (juridical) rights of animals and our moral duties towards them have changed. With this development, procedures involving animal harm have been considered increasingly morally problematic — more and more, they have come to be regarded as requiring justification. The ongoing intensive use of animals creates a tension between the rising moral standing of animals and consequent desire to protect them, on one side, and the benefits (eg dairy products, research-based knowledge) acquired through our use of animals, on the other.

The third historical development revolves around the proposal that the tension described above can be eased using our recently acquired biotechnological ability to manipulate the genome of animals (eg DNA-microinjection, embryonic stem cell mediated gene-transfer, SCNT-cloning and genetic engineering with nuclease-systems such as CRISPR/Cas) to create animals that are 'better suited' for human purposes. Hence, scientific progress, and the advent of modern biotechnology, has not just given us new opportunities for animal use. It has also introduced an opportunity to reduce animal suffering in various areas of human — in other words, our — animal use. For example, it has been suggested that we should use congenitally blind chickens in order to reduce injurious pecking in the flock (Sandøe *et al* 2014). Hornless cows have been engineered to render the painful cutting off their horns via de-horning obsolete (Carlson *et al* 2016). These measures are designed to reduce farm animals' infliction of pain on each other. By contrast, genetic animal disenhancement aims, not to modify external traits and the behavioural tendencies and capabilities of animals, but rather to reduce or eliminate the animals' ability to experience pain and suffering itself: it reduces the animals' experience of negative emotional states by limiting their *capacity* to have those states (Ferrari 2006; Shriver 2015; Devolder & Eggel 2019; Eggel & Camenzind 2020).



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## Paradigm shift with the latest technological developments: From thought experiment to realistic possibility?

GPD to reduce animal suffering seems feasible following recent technological developments in genetic engineering such as clustered regularly interspaced short palindromic repeats-CRISPR associated proteins (CRISPR-Cas), zinc finger nucleases (ZFN) and transcription activator-like effector nucleases (TALENs).

These breakthroughs in gene editing technology have added significantly to the options available where genetic alteration of animal genotypes and phenotypes is concerned. They function like 'molecular scissors' (ie custom-made designer nucleases) capable of targeting a specific DNA sequence and inducing a precise DNA break. Compared with previous biotechnological methods, the new techniques are claimed to be easier to use, cheaper and very precise (although this is also a feature of older methods). Perhaps most importantly, unlike previous biotechnological methods, and their limited application to different species, the new generation nuclease systems have been applied in several species and have so far proven adaptable (Shriver 2009, 2018). Thus, they appear to offer unprecedented possibilities.

Importantly, according to an account of recent advances in genetic engineering given by Shriver, particular enzymes and peptides have been identified that relate directly to what is considered the 'affective dimension of pain' — in other words, to 'caring about' the painful sensation. For example, studies in mice have shown a link between the affective dimension of pain and the AC1 and AC8 enzymes, the peptide P311 (Shriver 2009). Interfering with these pathways could potentially reduce the affective dimension of pain and/or chronic pain symptoms while leaving the acute pain response intact (Shriver 2009). Hence, what once was considered a mere thought experiment might already be, or soon become, a realistic possibility. This means, of course, that careful reflection on the potential ethical issues associated with GPD is becoming urgent.

## GPD in the light of the 3Rs principles

Would GPD comply with the principles of Replacement, Refinement and Reduction? The implications of GPD for animal research have previously been considered (Shriver 2015), and in the course of this discussion some attention was given to the 3Rs principles (eg Ferrari 2006; Devolder & Eggel 2019; Eggel & Camenzind 2020). However, we propose to systematically analyse the relationship between GPD and each principle separately. We shall use the ethical position of Russell and Burch as a normative standard of evaluation. Approaching the issues in this way, we aim to gain an insight into whether GPD is compatible with (one, two, or all three of) the 3Rs principles. We will also seek to obtain a better understanding of the normative underpinning of the 3Rs principles, and the conceptual and practical limitations that follow from this in the context of contemporary biotechnological developments.

### GPD and replacement

According to Russell and Burch (1959; p 70) sentient animals can be replaced in two different ways. That is, they distinguish between *absolute* and *relative* Replacement. Absolute Replacement is described by Russell and Burch as the "absolute ideal" (1959; p 70). Today, it includes the substitution of animal models with non-animal methods such as organs-on-a-chip, high-throughput systems (HTC), mathematical models and computational modelling, systematic literature reviews or the use of human volunteers (among many other methods). Partial and relative Replacement (and also comparative substitution) involve animal-derived material such as organoids, cells or fluids and "animals that are lower on the phylogenetic scale" (Institute for Laboratory Animal Research [ILAR] 2011; p 5). The latter may be invertebrates (eg *Drosophila melanogaster* or the amoeba [*Dictyostelium discoideum*]) or lower vertebrates. Additionally, relative Replacement involves "non-recovery experiments on living and intact but completely anaesthetised animals" and the use of painlessly killed animals (Russell & Burch 1959; p 71).

The rationale for using lower vertebrates is that these animals are believed to be "less sentient", thereby possessing a lower capacity to suffer compared to the higher vertebrates (the same distinction could be made among higher and lower vertebrates). Here, we should note that Russell and Burch did not explicitly discuss exactly what "less sentient" means, or the evidence on which ascriptions of it are based (Redmond 2019; p 656). From a sentientist perspective it is reasonable to substitute animals which display clear evidence of sentience with animals whose possession of sentience is less well evidenced. However, Russell and Burch have cautioned against the use of the evolutionary *scala naturae* as a norm from which guiding moral principles of animal research can be derived (ILAR 2011 and Blumer 2004; p 28 argue in this line). We also know now, from the case of cephalopods and crustaceans, that the emergence of sentience did not follow a single evolutionary lineage (Godfrey-Smith 2016), so the idea that determinations of sentience can be based on a *scala naturae* is highly questionable.

More importantly, relative Replacement cannot be accurately said to solve the moral problem of animal distress. Rather, it shifts it to the replacement animals. Although they are (allegedly) less sentient than the animals they replace, they remain sentient. Thus, they are capable of experiencing positive and negative mental states. The degree to which GPD affects other negative mental states, such as anxiety, fear and boredom, is crucial in any serious assessment of GPD as a relative Replacement method. Since it still involves the use of animals, GPD will be compatible only with relative or partial Replacement, not absolute Replacement, however among the relative Replacement methods GPD is unique, because it assumes that genetically disenhanced animals are unable to experience pain but capable, nonetheless, of experiencing positive mental states.

### GPD and reduction

As originally conceived by Russell and Burch, Reduction is not concerned with reducing the total number of animals in animal research *per se*, but only tries to minimise the number of animals for a specific experiment with a specific goal. Regarding this, a sufficient number of animals is the number that allows us, with the required statistical power, to answer a specific study question. We can call this "relative Reduction." An alternate interpretation would be to say that Reduction aims to reduce the total number of animals in animal research *per se* (see Ferrari 2006). We call this "absolute Reduction."

Where relative Reduction is concerned, the generation of GPD animals neither promotes nor obstructs Reduction, since relative Reduction is only concerned with the correct number of animals to reach a specific study aim.

The claim that GPD research (and GMO research generally) will lead to greater numbers of animals being used in research, and the inference that it therefore introduces a conflict between the goals of Reduction and Refinement, rests on a particular understanding of Reduction as "absolute Reduction." Only from an absolute Reduction perspective (one that goes beyond the original 3Rs framework) can it be questioned whether an effort to minimise harm and suffering (ie Refinement) which at the same time could, theoretically, lead to increased animal use is morally acceptable.

### GPD and refinement

Refinement is defined as "any decrease in the incidence or severity of inhumane procedures." Russell and Burch add that "its object is simply to reduce to an absolute minimum the amount of distress imposed on those animals that are still used" (Russell & Burch 1959; p 64, 134). It is the *ultima ratio* method within the 3Rs principles, and is applied after the other two Rs have been applied.

Refinement is usually taken to refer to animal housing and husbandry conditions, experimental procedures and the handling of the animals, experimental design, conduct and reporting, and also animal models (Herrmann 2019). *Prima facie*, with its potential to significantly reduce animal suffering, GPD is morally desirable from a Refinement point of view. However, this depends on the assumption that GPD animals are not more likely to sustain increased injuries, such as bruising, which may adversely affect the animal's well-being, than animals without GPD.

Here, the situation is not entirely straightforward. Studies have shown, on the one hand, that eliminating the affective pain dimension (ie the negative subjective experience of pain) does not impair acute responses to noxious stimulation (Ploner *et al* 1999). Thus, GPD animals are likely to continue to exhibit normal guarding behaviour (ie behaviour involving the avoidance of activities normally causing pain), making an increase in self-injuries unlikely. Moreover, even if bruises should result from such guarding behaviour, the bruises themselves would not cause any substantial suffering. From a purely sentientist point of view (where only negative subjective experiences are considered morally relevant) bruising will not be morally problematic anyway, even if the animals injure themselves more often, and even if the injuries have negative consequences, such as broken bones, limping and so on, as long as these consequences do not cause pain or suffering (Devolder & Eggel 2019).

Offsetting these considerations is the fact that humans with pain insensitivity disorder are significantly more vulnerable to physical injuries — they have a higher morbidity and mortality rate than the average for the population as a whole (Majeed *et al* 2018). Where GPD animals (eg mice or rodents) are social animals, the disenhancement may also have an impact on the social behaviour of the animals (Eggel & Camenzind 2020). How GPD affects the organism as a whole and the social behaviour of animal groups is yet to be properly investigated. What is clear is that in order to comply with Russell and Burch's sentientism, GPD must not have any negative (subjective) effects on the animals. Thus, the technology used to create GPD animals needs to be able to effectively manipulate the pain perception of animals without causing negative subjective side-effects.

Taking all of the above considerations together, we can see that within the science-centered, sentientist normative framework of the 3Rs principles, the generation of GPD animals is acceptable: in principle the use of such animals is compatible, at least, with relative Replacement and Refinement, while being value-neutral as regards Reduction. This conclusion is sound provided that GPD actually works and so long as the GPD animals do not suffer more than their unaltered kin and are still able to have positive emotions.

Of course, this raises the question as to whether the sentientist understanding of harm is an oversimplification, or questionable reduction of the moral issues at stake. Therefore, we shall now reflect on the ethical foundations of the 3Rs principles and elaborate what we consider to be the shortcomings of the 3R principles as a contemporary framework for morally acceptable conduct in animal research.

## The 3Rs under ethical scrutiny

### Limited moral significance of animals

One criticism concerns the moral significance ascribed to animals within the hierarchical sentientism of Russell and Burch. Notwithstanding our argument — and *pace* Vorstenbosch — animals do have a moral standing of their own within the 3Rs. However, we share Vorstenbosch's assessement, that the decisions about animal use in science are primarily a matter of science and scientists (Vorstenbosch 2005; p 343). This means that even trivial scientific interests could justify severe stress for a large number of animals which will eventually be killed. This criticism is not new, and has led to the implementation of a harm-benefit analysis (HBA) in the approval process for animal research in many countries around the world. While, according to the 3Rs principles, all experiments that are scientifically sound and necessary (ie instrumentally essential) are morally permissible, the implementation of HBA represents a paradigm change.



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Here, experiments that are scientifically sound and considered necessary can still be morally prohibited if the harm they inflict is disproportionate to the expected knowledge gain (goal-related essentiality). The extent to which an HBA, over and above mere compliance with the 3Rs, improves ethical evaluation critically depends, of course, on the underlying concept of harm used in the HBA, and on the moral significance given to animals. This means that for an HBA to actually represent a paradigm change in practice, not just theory, significantly more moral weight has to be given to animals than they were accorded within the 3Rs.

## The limited harm concept

In the ongoing discussion of GPD, a central issue concerns the concept of 'harm' and the question whether GPD animals are 'worse off' than normal species members (Ferrari 2006; Thompson 2008; Shriver 2009; Palmer 2011; Fischer 2020). This issue arises because there is a fundamental ethical distinction between sentientist and non-sentientist notions of harm. The question of morally relevant goods is also relevant to the moral assessment of the 3R principles.

While GPD will potentially reduce negative subjective experience in animals, it also raises questions about objective forms of harm and the possibility of harmless wrongs. Non-sentientists claim that the subjectivist harm concept employed in the 3Rs principles is too narrow, and that other morally relevant properties exist going beyond merely subjective harms. For example, altering an animal's *telos* (Rollin 1986, 1996) or violating its integrity (Rutgers & Heeger 1999) is a morally significant act. Unlike sentientist harms, non-sentientist harms include harms that do not cause subjective experience in the affected individual (Rippe 2008). An example of non-sentientist harm and harmless wrongdoing can also be found in the concept of dignity that is used in the Swiss Animal Welfare Act (Anonymous 2017). In this act, negative impacts on animals are defined to include not only pain, suffering and anxiety, but also major interference with the animal's appearance or abilities (non-sentientist harms) or excessive instrumentalisation and humiliation (harmless wrongdoing).

The word 'instrumentalisation' here refers to ways of using animals that fail to reflect the fact that the animals have value in themselves and are more than mere means to human ends. GPD could potentially be an example of impermissible instrumentalisation because it changes the abilities of animals in ways that do not take the animal's inherent value sufficiently into account. It is important to stress at this point that we are not claiming that the Swiss dignity concept is flawless or superior to the 3Rs in general. Our goal is merely to point out that, with recent developments in bioethics, the 3Rs have been rightly criticised as being too narrow in their conception of harm and assumptions about what is morally relevant.

The problem of instrumentalisation arises especially clearly in connection with so-called 'waste', or 'surplus', animals. It is to this matter that we now turn.

## Death and flourishing

Russell and Burch mention the death, killing and euthanasia of animals several times in their book. However, the topic is not discussed from a moral perspective and hence the death of research animals does not seem to represent a moral problem according to the authors. Humane (ie pain-free) killing is compatible with their sentientist approach. As long as the animals are killed with the least harm necessary there is no moral problem. However, this position has been objected to by critics who claim that death as such, and premature death especially, frustrate flourishing and hence represent a harm by deprivation. The moral importance of killing animals, and of animal death more generally, is clear, because in animal research the number of animals that are killed without ever having been used in an experiment (eg waste animals, breeding animals and surplus animals) is significant. Hence, we believe that the 3Rs, in Russell and Burch's formulation of them, neglect an important aspect of animal research.

We can distinguish two different types of surplus animal: those used exclusively for breeding (this includes animals used in the generation of GPD animals) and those which, after being bred, are not used in experiments.

Although this problem was recognised a long time ago in the debate about animal disenhancement (Macer 1989), it is neglected in current discussion of GPD and animal research in general. Hence, the actual debate over GPD underestimates the complexity of ethical issues raised by animal research and modern biotechnology. It is difficult to estimate the numbers of animals required for research into GPD and the eventual generation of GPD animals, but we think it is safe to say that this number would be considerable.

To neglect the deaths of these animals is problematic, because within the sentientist approach of the 3Rs the pain and suffering of every animal should count.

Furthermore, flourishing is an important element in modern interpretations of the Refinement principle. Whereas Russell and Burch were only concerned with the avoidance of negative subjective experiences, modern interpretations of Refinement include the promotion of positive experiences for research animals (eg play made possible by environmental enrichment).

## Refinement for its own sake?

Within Russell and Burch's hierarchical sentientism, human interests have lexical priority over animal interests. The instrumentalisation of animals for the benefit of humans is morally permitted, but whether we are permitted to use an animal for another animal's sake is not clear at all. From Russell and Burch's perspective nothing can be concluded about the relations between animals themselves. Given this, we might ask: Is it morally permissible to cause pain and suffering to animals during the development of GPD to prevent future pain and suffering in GPD animals?

There seems to be no clear-cut answer to this question, even outside the framework of the 3Rs. Interestingly, however, in Switzerland a project proposing to investigate the unknown harms of a planned procedure to improve future study designs

was refused a license with the explanation that "studies solely to improve the design of future experiments were unwarranted" (Anonymous 2019). Here, the officials decided, in effect, that Refinement for Refinement's sake is unjustified.

## Conclusion

GPD, and modern biotechnology more generally, interferes with animals' lives and abilities in ways going well beyond what was possible in 1959 when the 3Rs principles were developed by Russell and Burch. Applications that could not have been foreseen then are now being developed, and ethical theories have been developed to respond to these developments. Our aim has been to investigate whether the 3Rs are able to deal with issues raised by modern animal research. To this end, we have used GPD as paradigmatic proxy for modern biotechnology — an approach that seemed especially suitable given that GPD is believed to be a promising method to further improve scientists' ability to satisfy the 3Rs. We have also analysed the normative groundwork of the 3Rs principles and applied it to the question of whether GPD is morally permissible.

We have shown that GPD could potentially be regarded as a relative Replacement and Refinement method, while being value-neutral as regards relative Reduction. Consequently, we conclude that the 3Rs principles favour GPD, and that only absolute Reduction provides a potential basis, within the 3Rs framework, for moral misgivings about GPD.

Importantly, we have argued that the 3Rs principles, with their sentientist concept of harm, oversimplify the complexity of the ethical issues raised by animal research and modern biotechnology. This is highlighted in the discussion on GPD, where there is a tendency to reduce the ethical issue to minimising pain and suffering, and thus to oversimplify the moral concerns there are about animal research.

In moral philosophy, when scrutinising a problem, it is often impossible to take every aspect into consideration. One has to define the most important issues and ignore (at least, for the time being) others. However, it is important that the moral aspects one focuses on still adequately represent the initial problem. That is, formulated solutions need to do more than fit the simplified problem. They should be equally valid when applied to the initial problem. Where this is not the case, and the formulated solution only fits the simplified model, a moral-philosophical artifact is produced.

In other words, the 3Rs principle, if applied to GPD alone (as a proxy for modern biotechnology), runs the risk of generating moral artifacts. Here, the problem with the 3Rs principles lies with their excessively narrow, sentientist concept of harm. This concept of harm limits moral concerns to those about the negative subjective experiences of animals. It ignores the fact that animals can also be wronged by excessive instrumentalisation, and interference with their abilities, and also the fact that animals' deaths as a harm of deprivation must also be taken into account. Finally, the 3Rs principles fail to take into consideration the numbers of animals (and their deaths) required to generate GPD animals.

Inadequacies in the 3Rs framework have been recognised previously. These have been sought to be remedied (at least, partially) by complementing the 3Rs with HBA. However, while HBA introduces some improvements — eg in bringing about paradigmatic change in not only the evaluation of scientific necessity, but also the proportionality of inflicted harms and expected knowledge gains — it often continues to suffer from many of the same problems as the 3Rs framework. According to the critique we mentioned above, HBA only represents an improvement to the extent that it takes non-sentient harms and harmless wrongdoing more fully into account than the 3Rs principles do — and in practice it often fails to do this to an appreciable extent.

In our interhuman relations, the avoidance of pain and suffering plays a crucial role, but our moral obligations are not simply a matter of not (subjectively) harming our fellow humans. Similarly, we might have a moral responsibility to also consider other aspects in our relations with research animals.

## Declaration of interest

None.

## References

**Anonymous** 2017 *Animal Welfare Act (SR 455).* www.admin.ch/opc/de/classified-compilation/ 20022103/index.html

**Anonymous** 2019 *Swiss researchers struggle to get animal experiments approved.* https://www.the-scientist.com/news-opinion/swiss-researchers-struggle-to-get-animalexperiments-approved—65293

**Bayne K, Ramachandra GS, Rivera EA and Wang J** 2015 The evolution of animal welfare and the 3Rs in Brazil, China, and India. *Journal of the American Association for Laboratory Animal Science 54(2)*: 181-191

**Bentham J** 1996 [1789] *An Introduction to the Principles of Morals and Legislation*. Clarendon Press: Oxford, UK

**Blumer K** 2004 Ethische Aspekte zu Tierversuchen und das Solitaritätsprinzip. Senatskommission für tierexperimentelle Forschung Deutsche Forschungsgemeinschaft (ed) *Tierversuche in der Forschung* pp 27-29. Lemmens Verlag- und Mediengesellschaft: Bonn, Germany. [Title translation: Ethical aspects of animal research and the principle of solidarity]

**Broady BA** 1998 *The Ethics of Biomedical Research. An International Perspective*. Oxford University Press: Oxford, UK

**Camenzind S** 2020 *Instrumentalisierung. Zur einer Grundkategorie der Ethik der Mensch-Tier-Beziehung*. Mentis: Paderborn, Germany. https://doi.org/10.30965/9783957437457. [Title translation: Instrumentalisation. A basic category of the ethics of human-animal interaction]

**Carlson DF, Lancto CA, Zang B, Kim ES, Walton M, Oldeschulte D, Seabury C, Sonstegard TS and Fahrenkrug SC** 2016 Production of hornless dairy cattle from genome-edited cell lines. *National Biotechnology 34*: 479-481. https://doi.org/10.1038/nbt.3560

**Comstock G** 1992 What obligations have scientists to transgenic animals? *Discussion paper by the Center for Biotechnology, Policy and Ethics*. Texas A&M University, College Station, TX, USA

**Comstock G** 2000 *Vexing Nature? On the Ethical Case Against Agricultural Biotechnology*. Kluwer Academic Publishers: Norwell, MA, USA



https://doi.org/10.7120/09627286.31.4.002 Published online by Cambridge University Press

**Devolder K and Eggel M** 2019 No pain, no gain? In defence of genetically disenhancing (most) research animals. *Animals 9(4)*: 154. https://doi.org/10.3390/ani9040154

**Eggel M and Camenzind S** 2020 Authorization of animal research proposals – a comparison of harm concepts in different European regulations. *Berliner und Münchener Tierärztliche Wochenschrift 133*: 270-278

**Ferrari A** 2006 Genetically modified laboratory animals in the name of the 3Rs? *ALTEX 23*: 294-307

**Ferrari A** 2008 *Genmaus & Co Gentechnisch veränderte Tiere in der Biomedizin*. Harald Fischer Verlag: Erlangen, Germany

**Fischer B** 2020 In defense of neural disenhancement to promote animal welfare. In: Johnson L, Fenton A and Shriver A (eds) *Neuroethics and Nonhuman Animals. Advances in Neuroethics* pp 135-150. Springer: Cham, Switzerland. https://doi.org/10.1007/978-3-030-31011-0_8

**Godfrey-Smith P** 2016 *Other Minds. The Octopus, the Sea, and the Deep Origins of Consciousness*. Farrar, Straus and Giroux: New York, NY, USA

**Grimm H** 2013 Ethik im Kontext des Tierversuchs. In: Binder R, Grimm H and Alzmann N (eds) *Wissenschaftliche Verantwortung im Tierversuch. Ein Handbuch für die Praxis* pp 23-54. Nomos: Baden-Baden, Germany. https://doi.org/10.5771/9783845250328-21 [Title translation: Scientific responsibility in animal experimentation – a handbook for practice]

**Grimm H, Camenzind S and Aigner A** 2016 Tierethik. In: Borgards R (ed) *Tiere. Kulturwissenschaftliches Handbuch* pp 78-97. Metzler: Stuttgart, Germany. [Title translation: Animal ethics. Animal study handbook]

**Herrmann K** 2019 Refinement on the way towards replacement: Are we doing what we can? In: Herrmann K and Kimberly J (eds) *Animal Experimentation: Working Towards a Paradigm Change* pp 3-64. Brill: Boston, USA. https://doi.org/10.1163/9789004391192_002

**Institute for Laboratory Animal Research (ILAR)** 2011 *Guide for the Care and Use of Laboratory Animals*. https://grants.nih.gov/grants/olaw/Guide-for-the-Care-and-Use-of-Laboratory-Animals.pdf

**Knight A** 2019 Critically evaluating animal research. In: Herrmann K and Kimberley J (eds) *Animal Experimentation: Working Towards a Paradigm Change* pp 321-340. Brill: Boston, USA. https://doi.org/10.1163/9789004391192_015

**Lafollette H and Shanks N** 1996 *Brute Science. Dilemmas of Animal Experimentation*. Routledge: London, UK

**Macer D** 1989 Uncertainties about 'painless' animals. *Bioethics 3*: 226-235. https://doi.org/10.1111/j.1467-8519.1989.tb00342.x

**Majeed MH, Ubaidulhag M, Rugnath A and Eriator I** 2018 Extreme ends of pain sensitivity in SCN9A mutation variants case report and literature review. *Innovations in Clinical Neuroscience (ICNS) 11-12(15)*: 33-35

**Nelson L** 1923 *System of Ethics*. Yale University Press: New Haven, CT, USA

**Olsson IAS, Franco NH, Weary DM and Sandøe P** 2012 The 3Rs principle – mind the ethical gap! *ALTEX Proceedings of the 8th World Congress on Alternatives and Animal Use in the Life Sciences* pp 333-336. Montreal, Canada. John Hopkins University Press: Baltimore, USA

**Palmer C** 2011 Animal disenhancement and the non-identity problem: a response to Thompson. *Nanoethics 5*: 43-48. https://doi.org/10.1007/s11569-011-0115-1

**Ploner M, Freund HJ and Schnitzler A** 1999 Pain affect without pain sensation in a patient with postcentral lesion. *Pain 81*: 211-214. https://doi.org/10.1016/S0304-3959(99)00012-3

**Redmond C** 2019 When is an alternative not an alternative? Supporting progress for absolute replacement of animals in science. In: Herrmann K and Kimberley J (eds) *Animal Experimentation: Working Towards a Paradigm Change* pp 654-672. Brill: Boston, USA. https://doi.org/10.1163/9789004391192_028

**Rippe KP** 2008 *Ethik im Ausserhumanen Berich*. Mentis: Paderborn, Germany. https://doi.org/10.30965/9783969750926. [Title translation: Ethics in the non-human realm]

**Rippe KP** 2009 Güterabwägungen im Tierversuchsbereich. Anmerkungen zu einem ethischen Paradigmenwechsel. *ALTEX 26*: 3-10. [Title translation: Weighing of interests in justifying animal experiments]

**Rollin BE** 1986 On telos and genetic manipulation. *Between the Species 2(14)*: 88-89. https://doi.org/10.15368/bts.1986v2n2.9

**Rollin BE** 1996 *The Frankenstein Syndrome. Ethical and Social Issues in the Genetic Engineering of Animals*. Cambridge University Press: Cambridge, UK. https://doi.org/10.1017/CBO9781139172806

**Russell WMS** 2005 The three Rs: Past, present and future. *Animal Welfare 14*: 279-286

**Russell WMS and Burch R** 1959 *The Principles of Humane Experimental Technique*. Methuen: London, UK

**Rutger B and Heeger R** 1999 Inherent worth and respect for animal integrity. In: Dol M (ed) *Recognising the Intrinsic Value of Animals* pp 41-51. Van Gorcum: Assen, Germany

**Ryder R** 1995 Animal genetic engineering and human progress. In Wheale P and McNally R (eds) *Animal Genetic Engineering: Of Pigs, Oncomice and Men* pp 1-16. Pluto Press: London, UK

**Sandøe P, Forsman B and Hansen AK** 1996 Transgenic animal: the need for an ethical dialogue. *Scandinavian Journal of Laboratory Animal Science 1*: 279-285

**Sandøe P, Hocking P, Förkman B, Haldane K, Kristensen H and Palmer C** 2014 The blind hen's challenge: Does it undermine the view that only welfare matters in our dealings with animals? *Environmental Values 23:* 727-742. https://doi.org/10.3197/096327114X13947900181950

**Salt H** 1980 [1892] *Animals' Rights. Considered in Relation to Social Progress*. Society for Animal Rights: Clarks Summit: PA, USA

**Schweitzer A** 1923 [1987] *The Philosophy of Civilization*. Prometheus: New York, NY, USA

**Shriver A** 2009 Knocking out pain in livestock: Can technology succeed where morality has stalled? *Neuroethics 2(3)*: 115-124. https://doi.org/10.1007/s12152-009-9048-6

**Shriver A** 2015 Would the elimination of the capacity to suffer solve ethical dilemmas in experimental animal research? In: Grace L, Illes J and Ohl F (eds) *Ethical Issues in Behavioral Neuroscience* pp 117-132. Springer: Berlin, Germany. https://doi.org/10.1007/7854_2014_318

**Shriver A and McConnachie E** 2018 Genetically modifying livestock for improved welfare: A path forward. *Journal of Agricultural and Environmental Ethics 31(2)*: 161-180. https://doi.org/10.1007/s10806-018-9719-6

**The National Centre for the Replacement (NC3R)** 2021 *Refinement and Reduction of Animal Research*. https://www.nc3rs.org.uk/the-3rs

**Thompson P** 2008 The opposite of enhancement: nanotechnology and the blind chicken problem. *Nanoethics 2(3)*: 305-316. https://doi.org/10.1007/s11569-008-0052-9

**Vorstenbosch JMG** 2005 The ethics of the Three Rs principle: a reconsideration. *Animal Welfare 14*: 339-345

**World Organisation for Animal Health (OIE)** 2010 *Terrestrial Animal Health Code*. https://www.oie.int/index.php?id=169&L=0&htmfile=chapitre_aw_research_education.htm