

# Research

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# on Primates –

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# an ethical

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**Report by the Swiss Committee**

**on Animal Experiments (SCAE)**

**and the Swiss Ethics Committee**

**on Non Human Biotechnology**

**(ECNH)**

# Evaluation

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# 1 Introduction

A Cantonal Committee on Animal Experiments was asked to evaluate an application to conduct an experiment on marmosets with a view to determining the long-term effects of social deprivation on young animals. The experiment constituted one phase of a long-term research project and followed on from previously authorised experiments. The aim of the researchers was to develop a primate model for research into depression. If such a model were successfully validated, it could pave the way for additional studies to improve our understanding of certain depressive conditions.

In the opinion of the Cantonal Committee on Animal Experiments responsible for the evaluation, such animal experiments must be approached with extreme caution because the experiment is part of a research project using primates as experimental animals, and such experiments are particularly distressing for animals on account of their long-term effects. The Cantonal Committee considered it important that the particular study evaluated is basic research. Hence the ma-

jority of Cantonal Committee members did not oppose authorisation of the experiment. However, concern was expressed with regard to the potential developments that such a primate model could produce. Should such a model prove successful, it could be used routinely for testing pharmacological agents and consequently result in a sharp rise in the number of experimental animals used.

The Cantonal Committee recommended that the experiment in question be authorised subject to various conditions to ensure animal protection. At the same time the committee requested the Cantonal Veterinary Office to consult the Swiss Commission on Animal Experiments (SCAE) to obtain a precautionary evaluation of the potential developments that had been the subject of concerns. The central question was the extent to which the use of primate models should, in principle, be permitted for the purposes of research into depression. Since the issue is primarily ethical, the SCAE requested the collaboration of the Swiss Ethics Committee on Non Human Biotechnology (ECNH). The two com-



### Swiss Committee on Animal Experiments

The Swiss Committee on Animal Experiments (SCAE) is a committee of experts appointed by the Federal Council to advise the Federal Veterinary Office on all matters related to animal experiments. It also advises the cantons on questions of principle and in the event of disputes.

### Swiss Ethics Committee on Non human Biotechnology

The Swiss Ethics Committee on Non Human Biotechnology (ECNH) advises the Federal Council and the authorities on legislation and enforcement from an ethical standpoint. It can also independently address topics of ethical relevance and submit recommendations on future legislation to the Federal Council. The ECNH works with other federal committees on wider issues. The Federal Council set up the ECNH as an independent committee of experts in April 1998.

mittees set up a joint working group between January and June 2005 to examine this question of principle for the two committees. Almost from the outset it became apparent to the working group that they needed to discuss not only the specific question of using primate models for research into depression, but also the general question of the ethical permissibility of experiments involving primates. They felt that the specific application could not be examined without considering the general issue. The deliberations of the working group provided a basis for discussion by both full committees.

The first part of this report presents the fundamental ethical positions on research using primates. The second part discusses the criteria for an evaluation of interests, while the last part lists the recommendations of the SCAE and the ECNH to the Federal Council and to the authorities responsible for authorisation. The ethical permissibility of primate experiments in the field of depression research is discussed in three successive stages. The first stage is to examine whether, on the grounds of fundamental ethical positions, an evaluation of interests is appropriate for experiments on primates. Assuming that an evaluation of interests is permissible the second stage of the discussion centres on whether the stress to which the animal is subjected is acceptable, irrespective of human interests. Proceeding based on the next hypothesis that the permissibility of subjecting animals to stress is a question of relevance proportionate to the intended research objective

rather than a question of acceptability, we come to the third step in the discussion: an evaluation of interests i.e. weighing up the human interests in the experiment against animal interests in freedom from distress.

## 2 Fundamental ethical positions on research using primates

### 2.1 Who counts morally?

The ethical evaluation of research on primates is contingent on the question of *who counts morally* i.e. whom we classify as requiring moral consideration. The committees weighed up various ethical positions that dictate fundamental approaches to the evaluation of primate research. For some members, the distinction between great apes and other primates plays a decisive role in the discussion on moral status. Biologically, the family of great anthropoid apes comprises humans, bonobos, chimpanzees, gorillas and orang-utans.<sup>1</sup>

This section covers only the aspects of positions that are regarded as particularly relevant for the discussion on primate research. The summary is intended to facilitate understanding of the criteria on which the discussion in the second part is based, dealing with the current question of assessing the permissibility of experiments involving marmosets in the field of depression research.

#### 2.1.1 Anthropocentric position

According to the anthropocentric position, only humans are accorded inalienable dignity. Two fundamental forms of anthropocentrism can be distinguished. The first accords special status to the human species but does not exclude that other living creatures are also moral objects. The fact that someone is human is a morally relevant constant in this position, called speciesism. The second basic form of anthropocentrism takes the view that humans, and only humans, are moral objects.

From the speciesism position it follows that primates are accorded no absolute dignity since only humans are worthy of such dignity. However, to justify this position it is necessary to demonstrate why humans are accorded dignity as *humans*. One argument which is cited in this regard is the image and likeness of God. But this argument is based on a special religious conviction. Another argument cites the characteristics that distinguish humans from all other living creatures. One problem of this argument is that

characteristics are unevenly distributed even within the human species and there are no characteristics that can be attributed equally to all humans.

Immanuel Kant is regarded as an exponent of this type of position. He associates dignity with cognitive faculties: all living creatures capable of cognitive reasoning and moral capability are accorded dignity. Kant assumed that on earth, only humans possess this attribute. If, however, it transpires that other living creatures also exhibit the same attributes, they should be accorded the same dignity. Even if there is no consensus on whether great anthropoid apes have reasoning capacity and moral capability, recent empirical studies point to conduct that can only be explained by these animals possessing such characteristics. Hence primates must be treated in the same way as humans who are unable to give consent. Therefore, research involving humans who are unable to give consent is only morally permissible if they themselves benefit from such research. Research for other purposes is not permitted. Therefore, primates too may not be used for experimen-





tal research if the purpose is not for their benefit. Whether this applies to primates outside the family of great apes is open to question.

The criticism against this position is based on the fact that dignity is associated with cognitive faculties, but why exactly these properties justify being accorded dignity remains unclear.

### 2.1.2 Pathocentric position

According to one form of pathocentric position, *all sentient forms of life* are part of the moral universe. The criterion for moral consideration is the capacity for feeling, and in particular the ability to feel pain and suffering. Living creatures with these characteristics are accorded an inherent moral value. They must be considered for their own sakes.

Pathocentrism offers one way of justifying the moral necessity of animal protection without having to take into account the benefits of animals for humans. The Swiss Law on Animal Protection is currently based essentially on a pathocentric approach. Vertebrates in particular, but also some other sentient animals (cephalopods and decapods), are protected against pain, suffering, anxiety and damage. This pathocentric approach is now being expanded through a refinement of Art. 120 of the Federal Constitution, requiring that consideration must be given to the dignity of creation.

The pathocentric position takes the view that the suffering of primates is

on a par with the suffering of all living creatures capable of suffering. Whether the imposition of suffering can be justified through an evaluation of interests is open to question. Pathocentrists who exclude an evaluation of interests regard all animal experiments as impermissible. Others support an evaluation of interests.

Two main objections are raised against the pathocentric position. The first emphasises that only the ability to make moral judgements makes creatures moral objects. Sentience alone is not sufficient. The other objection takes the view that non-sentient creatures can also be subjected to harm. The group of creatures to be accorded moral consideration is therefore too small.

### 2.1.3 Biocentric position

Biocentrism places the concept of life at the centre of any moral consideration. It accords moral value to *all living creatures*. In its widest sense – *de facto* as well as beyond the factual – biocentrism was advocated by Albert Schweitzer in his formula of «reverence for life» as an ethical principle. According to this principle, all forms of life – human, animal and vegetable – must be accorded equal reverence in order to preserve and sustain life and the quality of life.

In addition to religious or mystical grounds, a philosophical rationale could be formulated, also *ex negativo*, for the biocentric position. The only access we have to other forms of life

and their faculties and sensitivities is via our own cognitive faculty of understanding, which is methodically based on analogy. The drawbacks of such access to other forms of life and the related conclusions are evident. Hence the biocentric position calls for other forms of life to be accorded the same respect as human beings, for as long as we are unable to know anything decisive about the capabilities and situations of other life forms which contradict this maxim.

The biocentric ethic and its ideal of according equal value to all forms of life is objected to on the grounds that humans are not effectively able to uphold the principle of biocentrism, i.e. they cannot avoid harming or destroying life on occasions. The associated inconsistencies facing human beings – thus goes the counter-argument – at most amount to the true tragedy of the human condition, namely that certain «necessities» of nature are unavoidable for humans. First and foremost the advocates of biocentrism could take the view that the unavoidable contradiction between the human reality and the human ideal must be endured, whilst coming as close as possible to the latter.

### 2.2 How much do those requiring moral consideration count?

After the question of *who* is to be accorded moral consideration, the second important question for determining the fundamental position is: *How much* do those to be accorded moral consideration (in our case, primates)

count? Depending on whether all members of the group to be accorded moral consideration are ascribed the same moral value or another – usually lesser – moral value than human beings, variants are described as egalitarian or hierarchical.

The *egalitarian variant* is based on the principle that, for all forms of life, aspects that are equal must be evaluated and treated equally and aspects that are unequal must be evaluated and treated unequally. So wherever other forms of life have the same interests as humans, they must be considered as equals.

According to the *hierarchical variant*, other forms of life deserve moral respect but not all equally. Either membership of the species counts i.e. if humans and animals have the same interests, humans are accorded priority. Or the complexity of characteristics counts i.e. the more similar the characteristics of the animals are (in terms of their complexity) to those of humans, the greater their moral relevance. The status of anthropoid apes plays a special role in the latter hierarchical variant. Some authors are of the opinion that anthropoid apes should be granted human rights. Others take the view that anthropoid apes and all other primates should be accorded high moral relevance, particularly in view of their cognitive faculties.

As already mentioned, the association of moral status with cognitive attributes is criticised because it is unclear why the complexity of char-



acteristics should be morally relevant. Against this objection it may be argued, on the one hand, that special value is ascribed to cognitive faculties because they have a significant influence on perception of and sensitivity to stress.<sup>2</sup> On the other hand, our understanding is hermeneutically preconditioned: our human perspective is unavoidable. Nevertheless, this is not incompatible with ascribing moral status to all non-human forms of life.

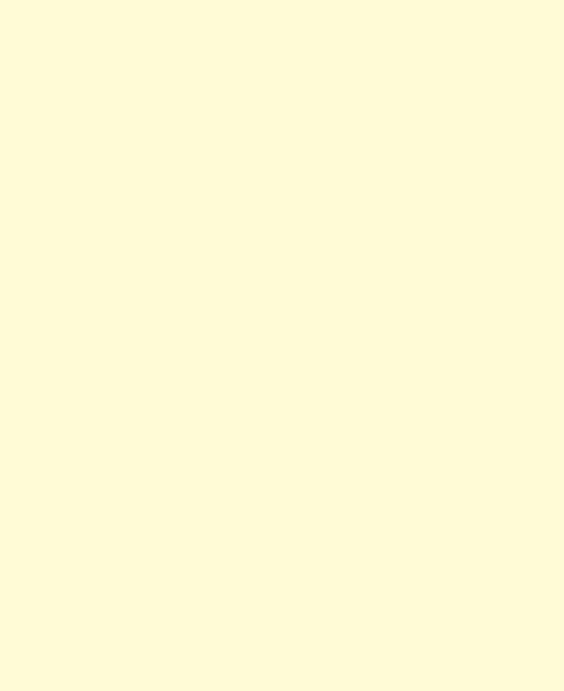
The hypothesis that large anthropoid apes have complex cognitive faculties, which are essentially comparable with those of humans, is based on strong indications. Yet among other primates we can observe complex social interactions and comparable stress behaviour when young animals are removed from their parents, and the ability to think ahead. According to the egalitarian view, these indications lead to the supposition that anthropoid apes and other primates have essentially the same interests as humans. Thus, according to the egalitarian variant, they must be accorded equal value and treatment. Therefore, the ban on instrumentalising humans for scientific experiments without their consent applies to all primates. According to the hierarchical variant, it is by virtue of their complex cognitive faculties that other primates should also be accorded a special moral status. The strong evidence of complex cognitive faculties provides no assurance that all primates should be counted among the moral community of humans. However, such evidence at least supports the view that no primate research

should be permitted as long as such uncertainty exists. From this standpoint, the burden of proof is reversed: anyone wishing to conduct research on primates must prove that the ethical objections are not valid. The burden of proof is on those who consider primates separate from the human – and hence the moral – community.

The call for a ban on primate research, in view of the uncertainty involved, is objected to on the grounds that this would impede the acquisition of new findings. This impediment is regarded in itself as ethically not permissible. On the other hand, it may be argued that a ban on primate research does not generally negate the legitimacy of knowledge acquisition. It simply questions *certain* research methods. It is necessary to examine other methods that could lead to this specific knowledge. It may be appropriate to refrain from any endeavour to acquire such knowledge if it can only be obtained in an unethical manner.

2.3 Fundamental positions within the committees

In the first step, members of both committees stated their positions on the question of *who* count morally i.e. who must be taken into consideration for their own sake. Does the category of those who must be accorded moral consideration cover only the human species? Is the category extended to anthropoid apes or to all primates? In the second step, positions were stated on the question of *how much* this moral consideration counts. In terms



of relevance, do comparable interests count equally (egalitarian variant) or do they count more in humans than in great apes or other primates (hierarchical variant)?

All members unanimously included humans, great apes and other primates among those deserving moral consideration. In so doing, the **large majority** took the hierarchical view. A **minority** advocated an egalitarian approach i.e. it accorded equal value to comparable interests in humans, anthropoid apes and primates.

From a hierarchical standpoint, the **majority** rated the comparable interests of humans higher than those of anthropoid apes, and comparable in-

terests of anthropoid apes higher than those of other primates. The **first minority** rated comparable interests of humans and anthropoid apes as equal, and those of primates as lower. The **second minority** rated comparable interests of humans higher than those of anthropoid apes and other primates, but accorded equal value to comparable interests of anthropoid apes and of other primates.

2.4 Conclusions

Due to their fundamental positions, a **clear majority** of members of both committees regarded any evaluation of interests as ethically not permissible for experiments involving anthropoid apes. Accordingly, this position

favours an absolute ban on experiments involving anthropoid apes. The **minority** did not exclude the possibility of an evaluation of interests for anthropoid apes. Whether a concrete experiment is permissible should also depend on an evaluation of interests in the case of anthropoid apes.

For all other primates, however, the **majority** regarded an evaluation of interests as permissible. The **minority** took the view that an evaluation of interests is also not appropriate and hence also not negotiable in the case of experiments on all other primates, on account of their cognitive faculties.

Egalitarian position and hierarchical positions					
Egalitarian position	humans	=	anthropoid apes	=	other primates
Hierarchical positions					
majority	humans	>	anthropoid apes	>	other primates
1st minority	humans	=	anthropoid apes	>	other primates
2nd minority	humans	>	anthropoid apes	=	other primates





# 3 Evaluation of interests for experiments on primates in the field of research into depression

## 3.1 Preamble

Under the terms of the current Law on Animal Protection, experiments on animals are negotiable but whether they are permissible must be decided on a case-by-case basis by means of the legally required evaluation of interests. However, from an ethical standpoint the majority of members of both committees reject the permissibility of experiments involving anthropoid apes. Only experiments involving other primates – which include the marmosets in the case under consideration – are regarded by the majority of members as suitable for an evaluation of interests.

## 3.2 Criteria for an evaluation of interests

An evaluation of interests must weigh the human interests in primate research against the stress to which the experimental animals are exposed or their interest in remaining free of stress. The higher the stress on animals is rated, the higher the requirements for grounds that justify the effect of such research on animals. It

must be noted here that we can adjust to a stress on humans (e.g. foregoing the benefits of such research), but the stress imposed on animals by humans is unavoidable for them. To this extent the evaluation of interests is distorted from the outset.

### 3.2.1 Stress for animals

#### Intervention and effects

In the experiment, which triggered the general discussion on primate experiments in the field of research into depression, the stress consists of separating the young marmosets repeatedly from their parents and socially isolating them (i.e. depriving them) between the second and 28th day of their lives i.e. during a phase of absolute dependency. In addition, the deprivation phases vary in length between 30 and 120 minutes. The marmosets are unable to predict either the time or the duration of the deprivation. Young animals are observed to enter a state of extreme distress during every intervention.

## Deprivation and privation

For the purposes of **deprivation** experiments, the young animal grows up with its biological parents but is separated from them unexpectedly at specific times. Deprivation of parental care triggers an acute stress reaction in young animals, which lessens over time, eventually decreasing to the level of the control animals. Only after multiple deprivations does the development curve change and from then on permanently deviate from the control animal curve. Their development is then comparable to the development observed in animals subjected to privation.

**Privation** involves removing the young animal from its biological mother at birth. It grows up in an environment which guarantees its survival. However, it is exposed to virtually none of the additional stimuli that a biological mother would normally provide. Privation has a dramatic effect on the animal's long-term development. The development curve of these animals follows the same course as the development curve of the control animals, but at another level.

The brain can adapt to an anticipated environment and, depending on age and species, develop within a defined bandwidth. In the experiments on marmosets, however, deprivation of parental care overtaxes the adaptability of the young animals' brains. The brain of a young animal subjected to deprivation changes over the long term. Even when at rest, for instance, the level of the stress hormone cortisol is increased compared to control animals. The basis for homeostasis has undergone permanent change. This fundamental condition can no longer be corrected; on the contrary, it is the aim of the experiment to induce it. Imposing excessive strain on the brain's adaptability provides the basis for examining the related short- and long-term effects in young animals.

Deprivation has a serious lifelong effect on the animal's behaviour, reactions and ability to learn. The extent of changed responses suggests that the animal's perceptions have been altered and that its ability to respond to social and environmental stimuli has decreased. The animals show symptoms comparable to those found in humans suffering from depression. However, no direct life-threatening effect or organic damage to the animals has been observed as a result of such intervention.

## Assessment of stress

According to Directive 1.04<sup>3</sup> issued by the Federal Veterinary Office, animal experiments are classified into four severity levels from 0–3:

- Severity Level 0 covers interventions and treatment that subjects animals to *no* pain, suffering, harm or severe anxiety and which do not significantly affect their general wellbeing. Examples from veterinary practice are taking blood for diagnostic purposes, or subcutaneous injections of a medicament.
- Severity Level 1 covers interventions and treatment that subject animals to *minor, short-term stress* (pain or harm). This includes the forced injection of a drug or the castration of male animals under an anaesthetic.
- Severity Level 2 covers interventions and treatment that subjects animals to *short-term, medium stress or medium- to long-term minor stress* (pain, suffering, harm, severe anxiety or a significant effect on general wellbeing). Examples from veterinary practice are operations on a broken leg bone or the castration of female animals. Examples in the field of neurology, psychiatry and behavioural biology include various forms of deprivation such as removal of feed, removal of water in the case of dry feed, removal of social partners for a defined period, or stress models without prior habituation e.g. exposing animals to permanent light (excessive stimulation).





- Severity Level 3 involves interventions or treatments that expose animals to *severe to very severe or medium- to long-term medium stress*. Examples from veterinary practice are terminal infectious diseases or cancers without timely euthanasia. Examples in the field of neurology, psychiatry and behavioural biology are the same forms of deprivation as listed under Severity Level 2 but over longer periods. Over-stimulation stress models in this Severity Level category are models with chronic and frequently-changing severe stress factors to which the animal is exposed at unpredictable intervals.

On the basis of this current classification of severity levels, the majority of members of the Cantonal Committee on Animal Experiments and the Cantonal Veterinary Office concluded that the experiment under review should be rated as Severity Level 2. While the *privation* method is rated as Severity Level 3 according to this directive, due to the lower impact the *deprivation* – in the opinion of the majority of the Cantonal Committee – is rated as less stressful for young animals and their parents. Notwithstanding this decision, both federal committees must evaluate the animal experiment under review as an exemplary case, irrespective of the prevailing law and practice and from an *ethical standpoint*, in order to formulate recommendations based on these deliberations for the purpose of future legislation. The following additional considerations also play an important role in the ethical evaluation.

Nowadays, privation is avoided in animal experiments since this form of intervention is regarded as distressing for the animals. It could be argued that deprivation constitutes a refinement of privation in terms of the 3 Rs (reduction, refinement, replacement). However, deprivation could also prove more distressing than privation since the continual switch between the parents' presence and absence instils fundamental anxiety. In the case under consideration, the determining factor for selection of privation or deprivation was not the stress imposed on the animals, but the relevance of the animal model for the human condition of depression. While cases of privation in young humans are also known, typical human behaviour in this context entails the neglect of children, which is more akin to deprivation. The aim of the experiments involving marmosets is to simulate this human behaviour as realistically as possible. The method of deprivation is therefore regarded as more scientifically relevant. However, the argument that deprivation constitutes a refinement of privation does not hold up.

Furthermore, the question arises as to whether depriving young animals highly dependent on their parents for research purposes constitutes excessive instrumentalisation and hence abuse of the dignity of creation in animals<sup>4</sup>. A refinement of this constitutional provision is to be included in the reformed Law on Animal Protection. The dignity of an animal is respected if a careful evaluation of interests justifies the stress imposed

on the animal. In their joint brochure published in 2001 and entitled "The Dignity of Animals", the ECNH and the SCAE stated that interventions in animals require justification if the animals are exposed to suffering, pain, harm or distress. This also includes changes in the animal's appearance (and capabilities), humiliation and excessive instrumentalisation. In terms of the instrumentalisation aspect, the interest of individual animals in their own existence i.e. their beneficial relationship with the environment must be assessed. Central to this relationship are the animal's development, preservation of existence and ability to reproduce. Against this backdrop it is necessary to examine whether the severity rating for animal experiments should be re-assessed, in particular for non-invasive animal experiments (without any physical harm); because even if the young marmosets in the experiment under consideration do not appear to be exposed to any major physical harm, they appear to suffer greatly.

In assessing the stress imposed on marmosets one is also faced with the question of whether self-awareness should be ascribed to primates. Self-awareness is defined as the ability to generate a synthesis (a type of picture or conceptualisation) of oneself when experiencing consecutive moments of awareness. Among other things, depression affects the social bonding abilities which are inordinately important for marmosets. However, it is difficult to imagine social bonding without any degree of self-aware-

ness. Moreover, self-awareness may be related to an enhanced perception of suffering. Whether such perception exists in primates is open to question. However, it is the opinion of the committees that primates must be handled with much greater care, and greater caution must be applied when examining applications for permits for experiments on primates. Moreover, consideration must be given to the fact that marmosets are used in research into depression because, as primates, they are closest to humans in terms of their social-familial structure, specific behavioural patterns, and neuro-physiological attributes. The experiment uses the deprivation procedure to trigger phenomena in the marmosets' brains that are comparable to those exhibited by humans with depressive symptoms. The aim is to develop a pharmacological form of treatment based on the neuro-biological findings. This begs the question of whether such research at the epistemic level is based on a *de facto* but non-explicit assumption of self-awareness on the part of the primates. However, this would mean justifying such research from a scientific standpoint without revealing that it is not ethically permissible.

#### Conclusions

On the basis of these considerations, the members of both committees **unanimously** came to the conclusion that the deprivation of marmosets and the related consequences for the young animals should in future be rated as Severity Level 3.





According to the ethical guidelines on animal experiments issued by the Swiss Academy for Medical Sciences (SAMW) and by the Swiss Academy for Natural Sciences (SCNAT), revised in 2005<sup>5</sup>, certain experimental situations may impose such severe suffering on animals that an evaluation of interests would always be weighted in favour of the animals. It is therefore necessary to refrain from such experiments even if this means having to forego the anticipated findings. This provision can only be taken to mean that these experiments must be regarded as unacceptable. Unacceptability excludes the possibility of an evaluation of interests.

For the **great majority** of members, the marmoset experiment is rated as Severity Level 3 and as such belongs to the category of experiments that impose severe suffering on animals and are hence unacceptable. According to this view, the permissibility of the experiments on marmosets fails to meet the *criterion of acceptability*<sup>6</sup>. *No matter what* human interests are involved, such experiments are ethically unacceptable. Hence any findings obtained in this way should be renounced. A **minority** of members is of the opinion that the permissibility of such harmful animal experiments is also a *question of appropriateness*. According to this minority opinion and under the terms of the current law, which does not recognise the criterion of acceptability, only the results of an evaluation of interests can determine whether or not an experiment is permissible.

### 3.2.2 Research aim

According to the research group the aim of the project is to gain a better understanding of the causes and mechanisms of depression. In earlier experiments the research group observed that the stress triggered in baby marmosets by removing them from their parents resulted in permanent physiological and behavioural changes in the animals. These changes are similar to certain symptoms and physiological characteristics associated with human depression<sup>7</sup>. The research group aims to develop a marmoset animal model in order to examine the various physiological, neuro-physiological and behavioural parameters which are regarded as relevant for human depression. If such a primate model is created, the research group hopes to be able to examine the following questions:

- The relationship between environment and genes, which associates stress in early life with persistent depression;
- The neurobiology of depression;
- The neurobiology of the pharmacological treatment of depression;
- Identification of a new receptor target for the treatment of depression.

The research group's rationale for the project has to be seen in a wider context: according to WHO estimates, 340 million people around the world suffer from depression. In Europe more people die from suicide than in road accidents. Even taking into account

the fact that some suicides are not attributable to depression or illness-related factors or any known causes, there is no question that depression is a life-threatening illness.

While acknowledging the need to distinguish between different forms and causes of depression, the committees unanimously view the general aim of finding a cure for human depression as important. They also recognise that a broad-based effort must be made in depression research in order to develop and promote treatment strategies.

### 3.2.3 Potential consequential problems

There is concern that at a later stage i.e. in an established marmoset model, tests would be conducted to study the effects of pharmacological agents. Fears that this would give rise to a sharp increase in experiments on primates also prompted the fundamental discussion on primate research.

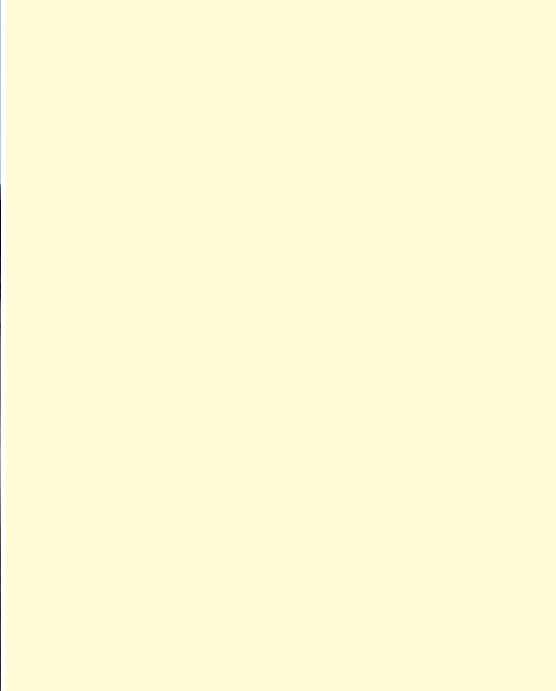
However, one counter-argument to the rise in primate experiments is the fact that primates are very expensive to keep. Should – as the research scientists are hoping – a receptor target be found, it is more likely that genetically modified rodents would be used to test pharmacological agents.

### 3.2.4 Scientific nature of the research project

Depression is a multifactorial illness involving a complex interaction of potential risk factors and triggering mechanisms. One recognised risk factor is separation from the parents at an early age, which can increase susceptibility to depression, resulting in repeated incidences of the illness and ultimately in chronic depression. Within the context of depression research for the human situation, depriving young marmosets of their parents and observing the long-term effects of this deprivation on these young animals appears to be a meaningful approach for the human situation.

Moreover, the research project under consideration is part of a European as well as a national research project. Recently, efforts have been made to integrate the project within an interdisciplinary framework. In addition, it complies with the international standards based on the three Rs (reduction, refinement, replacement). Measured by *disciplinary* standards, the experiment methodology is deemed *suitable*. However, in view of the wider research issue and the high level of stress to which animals are exposed the committees criticised the lack of effective interdisciplinary collaboration. In the view of the committees, an interdisciplinary evaluation must be explicitly required by law and accordingly incorporated into evaluation practice.





From an ethical standpoint, it is also essential to determine whether the selected research approach is *adequate* in view of the complexity of the illness. This is open to question for the following reasons: Despite the substantial volume of information already available, depression largely evades any measurable scientific examination. Depression is a highly complex condition, the causes of which are still largely unknown. Depression is described as a group of symptoms rather than being defined *per se*. Even if people suffer from depressive disorders and exhibit comparable symptoms, they react in highly individual ways to identical or comparable situations which are known to trigger depression. Psychological experiences cannot be reduced to mere neuro-physiological processes. Cultural background also plays a significant role. The research project under consideration is therefore criticised for adopting a reductionist approach to the complexity of the illness.

This criticism is objected to on the grounds that the research project does not attempt to cover the full complexity of all the factors related to depression. Research findings to date have shown that depression is a multifactorial illness comprising not only psychological but also physiological (neuro-physiological and neuro-chemical) factors. The research project under discussion is endeavouring to identify these factors accurately with the aim of examining individual aspects which could prove relevant in developing a pharmacological approach to

treatment. The fact that this type of research for pharmaceuticals has proven highly successful in the past is cited in support of this argument. Nevertheless, the chances of the experiment under discussion succeeding cannot be assumed on the basis of this general statement on past achievements.

The clinical relevance of animal studies for psychiatry must also be assessed. While critics of animal experiments, including some members of the psychiatric profession, seriously doubt the clinical relevance of such studies, they are strongly supported by other members of the psychiatric profession and by research scientists. They consider the data obtained from animal experiments highly relevant in terms of identifying the neuro-physiological factors of depression. Nevertheless, there is general consensus that the interdisciplinary exchange of information could be stepped up and that efforts should be made to this end.

However, based on the collected scientific information and on internal expertise, members of both interdisciplinary committees **unanimously** (with four abstentions) questioned the relevance of the marmoset animal model to provide any meaningful findings for research into depression.

### 3.2.5 Research project's chances of success

Since the research project imposes severe stress on the experimental animals, it is important for the purposes of an ethical evaluation of interests to determine the probability of the project's success. A huge body of data is already available in the field of depression research. A large number of hypotheses have already been excluded as a result of research to date. Hopes that the objective is in sight are understandable, but may be false. Despite huge volumes of data, the causes of depression remain largely unknown. There is no definition of the disease: merely a list of symptoms. As a result, it can also be argued that a breakthrough is far from imminent and the light at the end of the research tunnel is still some way off.

The chances of success for this research project are difficult to quantify. However, from an ethical standpoint they must be foreseeable in order to justify the severity of the stress imposed on the primates. Nevertheless, to some extent uncertainty is an inherent part of any research undertaking and *in itself* is not a sufficient criterion by which to determine the relevance of a research project.

### 3.2.6 Alternative approaches in depression research

In the field of research into depression, animal experiments in general and primate experiments in particular are primarily justified on the grounds that studies on humans are extremely lengthy and costly, or in many cases ethically impermissible. In view of the severity of the stress imposed on experimental primates, however, it is necessary from an ethical standpoint to examine the possibility of alternative approaches.

Such alternatives must permit identical or comparable meaningful results to be obtained. Yet it is difficult to do an objective comparison of different research approaches. Specialist research scientists generally have expertise in a particular research field. This may prejudice them in favour of work in their own field. It is therefore essential that research projects be subjected to interdisciplinary evaluation and compared against other research approaches.

Given the complexity of human depression and the huge disparity in individual patients' symptoms, the course of their illness, co-morbidity, need for treatment and side-effects of pharmacological substances, it is necessary in particular to examine the possibility of direct studies on humans. In addition to less invasive blood and urine examinations, neuropsychological studies combined with imaging techniques such as functional Magnetic Resonance Imaging (fMRI)<sup>8</sup> and Nucle-





ar Magnetic Resonance (NMR) Spectroscopy<sup>9</sup> can play an important role. In addition, studies involving humans also provide depression research with a linguistic aspect, which is missing in animal models.

If, however, no alternative research approaches are found, this may necessitate foregoing the opportunity to obtain findings if experimental animals are exposed to unreasonable stress, even if these findings cannot be obtained in any other way.

### 3.3 Evaluation of interests

#### 3.3.1 Premises on which the evaluation of interests is based

The stress to which animals are exposed – or their interest in remaining free of such stress – was weighed against the human interests in the experiment on the premise that such an evaluation is appropriate for primate experiments. The majority of members of both committees adopted this premise (see section 2.4). On the other hand, a minority of members generally precluded the negotiability of experiments on primates on account of their cognitive and emotional abilities.

The evaluation of interests may not be pursued if the stress to which the animals are exposed in the marmoset experiments is assessed as unacceptable. The majority of members rated the stress to which young marmosets are exposed through deprivation as unacceptable (see Section 3.2.1). The minority rejected any such unacceptability criterion in the case of primates, and took the view that the severity of the stress is always measured in relation to the intended benefit. According to this minority view, only the results of an evaluation of interests can provide information on whether such stress is appropriate and therefore whether such experiments are permissible. The following section outlines an evaluation of interests in accordance with this minority position.



#### 3.3.2 Results of the evaluation of interests according to the minority position

- The **majority** took the view that the work involving the marmoset model and related applications pursue an important objective i.e. obtaining additional results on depression. The **minority** was unable to provide an assessment in this regard. Four members abstained from this vote.
- The **majority** rated the chances of such an animal model being successfully developed as relatively low, while one **minority** rated them as medium, and another **minority** felt unable to judge this point.
- The **majority** felt unable to assess whether or not equivalent or comparable research alternatives to the marmoset model exist. The **minority** believed that such alternatives are available.
- The stress to which the animals would be exposed was rated **unanimously** (with one abstention) as high.
- The members also took the **unanimous** view that the high level of stress outweighed the intended benefit and hence rendered the experiment unjustifiable.

Members of both committees therefore came to the **unanimous** conclusion that the stress to which primates are exposed in the experiment under discussion (creation of and work with a marmoset model by means of deprivation) is unreasonable and that consequently this research approach should be refrained from.

#### 3.3.3 Requirements regarding institutional structures

If a question can only be effectively answered on an interdisciplinary basis, then, from a scientific standpoint, not only a mono-disciplinary research approach but also a monodisciplinary assessment of the research experiment are insufficient. An appropriate level of interdisciplinarity in evaluating experiments must be achieved in order to ensure the scientific relevance of the evaluation findings. Hence it follows that the organs responsible for authorising experiments must be equipped with the requisite professional expertise.





# 4 Recommendations

On the basis of their deliberations, the two committees **unanimously** make the following recommendations:

**Legislative:**

- 1. Experiments on anthropoid apes (great apes) should be explicitly prohibited, even though no such experiments are currently being conducted in Switzerland. Severity Level 0 experiments should be exempted from this ban.
- 2. Any evaluation of the permissibility of primate experiments must be subjected to an interdisciplinary review. The law must therefore provide for such an interdisciplinary review of the scientific relevance of such experiments and their research objectives.
- 3. A study should be conducted to determine whether the cantonal organs responsible for examining applications and authorising permits have at their disposal the relevant breadth of expertise, and whether institutional changes are required. In view of the low number of experiments conducted in this field, the possibility of charging

ing the Swiss Committee on Animal Experiments (SCAE) with responsibility for evaluating all such experiments should be examined. In this case it would be necessary to determine how interdisciplinary expertise, and in particular ethical expertise, could be guaranteed within the SCAE.

**Authorisation:**

4. Due to their close similarities to humans and their cognitive faculties, primates should be accorded a special status. For ethical reasons the competent authorities should – within their current scope – only permit experiments involving primates with the utmost restraint.

5. Deprivation must not be taken to mean a refinement of privation in the sense of animal welfare.

**Research policy:**

6. The development of alternatives in depression research must be encouraged.

**Research funding:**

7. Research into depression should take into account the multifactorial aspects of depression and not be conducted on a monofactorial basis. All institutions involved in funding research should therefore be urged to insist that applicants ensure that research projects are backed by a good interdisciplinary network.

8. Institutions involved in funding research should not authorise any primate experiments without requesting an ethical evaluation.



- 1 *Gibbon apes are occasionally referred to as small anthropoid apes to distinguish them from great anthropoid apes. However, this document does not adopt this distinction: gibbons are included among other primates.*
- 2 *In certain situations, some living creatures can suffer more from a comparable stress than creatures with lesser cognitive faculties, for example if they clearly recognise their inability to influence or evade the situation and therefore suffer all the more due to this awareness. In other situations, however, this reflexive ability may also lessen the distress, for example the knowledge that the pain is temporary, that painful treatment can be discontinued or that it can lead to an improvement in the long term.*
- 3 *Animal Welfare Information 1.04, Federal Veterinary Office, with general guidelines and examples of classification of animal experiments according to stress categories (in German and French) see [www.bvet.admin.ch](http://www.bvet.admin.ch), key-words Tierschutz (protection des animaux) / Tierversuche (expériences sur animaux).*
- 4 *Article 120 of the Swiss Federal Constitution stipulates that the dignity of creation must be respected for animals, plants and other organisms. In the opinion of the ECNH and the SCAE, the dignity of creation does not imply absolute protection. The dignity of creation in animals is respected if interventions can be justified under the terms of a careful evaluation of interests. It is not respected if an evaluation of interests concludes that the interests of the animal outweigh the opposing (human) interests.*
- 5 *[www.samw.ch](http://www.samw.ch), [www.scnat.ch](http://www.scnat.ch).*
- 6 *In case the experiment is not adopted as unacceptable, the committees also examined the question of further breeding of these experimental animals. The members were of the unanimous opinion that if such irreversibly damaged animals are capable of breeding,*

*they should nevertheless not be used for further breeding. Art 16, para. 5 of the Law on Animal Protection requires that animals who can only live on in suffering after an intervention be euthanised at the earliest opportunity.*

7 *In that case, the question is whether it would be more appropriate to refer to post-traumatic stress.*

8 *Functional Magnetic Resonance Imaging (fMRI) uses magnetic fields to identify and visualize parts of the brain that respond to specific physical stimuli or activities. This is done by means of an MRI scanner that displays the increase in bloodflow to activated regions of the brain.*

9 *Nuclear magnetic resonance (NMR) spectroscopy uses the interaction between electromagnetic waves with material to examine its physical, chemical and biological properties.*

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July 2007 (reprint of May 2006)

Publisher: Swiss Ethics Committee on Non-human Biotechnology (ECNH) and Swiss Committee on Animal Experiments (SCAE)

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Graphic design: Atelier Bundi, Boll

Printing: Ackermanndruck AG, Berne

This report is available in printed form in English, French and German. It is also available in electronic form, in these languages and in Italian, at [www.ekah.ch](http://www.ekah.ch).

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Printed on chlorine-free bleached paper.



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