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Animal Experimentation in Research

Statement on the Transposition
of EU Directive 2010/63 into German Law

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Preliminary Remarks

Advances in biological and medical research are largely based on work involving animal experimentation. Whilst the development of alternative methods is gathering pace, current research is nonetheless inconceivable without using methods that involve animal experimentation.

The social and political debate and the balancing of legal interests – such as freedom of research, the State's duty of care towards its citizens and animal protection – have resulted in Germany having one of the world's strictest bodies of animal protection law. As part of the pan-European harmonisation process, it has become necessary to reform this legislation in a comprehensive manner.

The core tasks of the Academy's Statements are to ascertain the pros and cons of difficult issues, to frame their scientific basis, and to present science-based recommendations for addressing the issue at hand. In the present Statement, the German Academy of Sciences Leopoldina and the Union of the German Academies of Sciences and Humanities engage in a much-debated issue of extraordinary social relevance.

The present Statement not only describes the ethical bases and the legal framework for animal experimentation research, but also focuses on the broader field of biological and medical research from various perspectives. Further, the practice of animal experimentation and its current state of development within research is examined, and a sensible and constructive transposition of EU law into German law is considered.

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Table of Contents

1. Summary

Background and General Issues

On 22 September 2010, the European Parliament and the Council of the European Union adopted a Directive on the protection of animals used for scientific purposes. This Directive was essentially intended to harmonise the significantly differing bodies of national law within the Member States, into which it was required to be transposed into national law before 10 November 2012. In Germany, a legislative and regulatory proposal was approved by the Cabinet on 23 May 2013.

The German National Academy of Sciences Leopoldina and the Union of the German Academies of Sciences and Humanities consider it their task to engage with this legislative process, which is of extraordinary importance for scientific animal experimentation and for Germany as a research location, with a spirit of constructive criticism. These institutions have accordingly prepared the present comprehensive Statement, the essential results of which are summarised below.

Animal experimentation is an important means of acquiring knowledge that continues to be an essential part of biological and medical research. Such experimentation is primarily pursued during research into complex phenomena that cannot be addressed using simpler and less ethically problematic trials – for example in relation to the question of whether a pharmaceutical lowers blood pressure. A significant share of animal experimentation is the direct or indirect result of statutory requirements in relation to the research, development and manufacturing of products and equipment in the fields of human, dental and veterinary medicine, as well as toxicological studies and other safety tests.

In the field of veterinary medicine, the results of animal experimentation are directly beneficial for animals, such as in research into animal diseases that afflict wild or breeding animals, or with regard to issues of reproduction and species conservation. Otherwise, animal experiments are overwhelmingly intended to benefit humans, such as in the development of vaccines and pharmaceuticals, or the improvement of surgical procedures and medical training. Significant progress in biology and medicine is the result of animal experiments. This includes vaccines, which have led to the complete or almost complete disappearance of infectious illnesses such as small pox and polio, along with highly effective pharmaceuticals used to combat high blood pressure, heart attacks and diabetes and assist with heart surgery, as well as life-saving medical technology such as defibrillators.

Although the results of animal experimentation cannot be transferred to humans indiscriminately, they do significantly improve the safety of the initial use of pharmaceuticals, operations and equipment on humans. Accordingly, the World Medical Association's Declaration of Helsinki states that *"Medical research involving human subjects must conform to generally accepted scientific principles [...] and, as appropriate, [be based on] animal experimentation."*

However, freedom of research and the protection of human health, both of

which are protected under German Basic Law, stand in opposition to the harm caused to animals through experimentation, the extent of which may vary widely, ranging from the mere observation of behaviour, to surgery and subsequently to killing. To minimise harm to animals and to replace, reduce and refine their use (the 3Rs Principle) has long been a recognised foundational principle for research and legislation.

Nevertheless, it is not easy to weigh the competing interests of knowledge acquisition and the protection of health on the one hand, and animal protection on the other hand. Such a process demands an ongoing conscious balancing of goals, both by individual scientists and also by society as a whole. To ensure that this does not lead to arbitrary results, clear ethical and legal guidelines are required, according to which the various involved legal interests are appropriately considered.

General Considerations

I. Animal protection is undoubtedly a highly significant legal interest, as attested by its inclusion in the declaration of State objectives in Article 20a of the Basic Law. However, animal experimentation is permitted for scientific purposes through the freedom of research guaranteed under Article 5(3) of the Basic Law. The individual position of the scientist under the Basic Law is bolstered by the duty on the State to protect human life and physical integrity (Article 2(2) of the Basic Law), while animal experimentation can be used to gain important basic medical knowledge, or even to develop particular diagnoses and therapies, especially in the field of human medicine. Animal protection law is thus required to strike an appropriate balance between the opposing legal interests of freedom of research and the protection of the general public's health on the one hand, and animal protection on the other hand.

II. All three legal interests referred to thus far have the same normative status, as they are all enshrined within the Basic Law. However, this does not mean that they effectively have the same weight when measured against one another. Indeed, it must be considered that animal protection is simply proclaimed as a general goal of the State, whilst freedom of research is framed as a classical defensive right against the State, and the State's duty to protect the life and health of the general public relates solely to humans. The issue at hand therefore involves an asymmetrical balancing under which the rights and claims of humans are granted structurally greater significance than the notion of ethical animal protection. Within a constitutional system centred on human dignity (Article 1(1) of the Basic Law), this predominance of human legal interests is firmly established. In principle, EU primary law involves the same assessments and balancing, although the focus on health protection is even more strongly accentuated.

III. Weighing the various legal interests with constitutional status falls primarily to the legislature. According to the theory of "substantive legislative reservation" *(Wesentlichkeitstheorie)* developed by the Federal Constitutional Court, the legislature is obliged to adopt all substantive provisions within basic normative areas, such as in relation to the exercise of constitutional rights. Article 80(1) of the Basic Law makes provision to the same effect by requiring that the content, purpose and scope of regulations be specified in the legislation-granting authority assigned to the secondary legislator. It follows that even the most important prerequisites under which basic constitutional rights may be impinged upon must be specified by formal legislation. This gives rise to significant concerns, as the draft legislation provides more than 20 authorisations to issue regulations, and as one of its central planks enables new restrictions on

freedom of research that were not specified sufficiently within the law to be imposed. All corresponding provisions of the draft legislation should thus be subject to a careful examination as to whether Article 80(1) of the Basic Law and the theory of substantive legislative reservation of the Federal Constitutional Court have been complied with. Particular attention should be dedicated to the frequently encountered authorisation to the secondary legislator to "implement the acts of European Union legislation" in order to ensure that this possibility does not result in the undermining of the Basic Law or the circumvention of parliamentary legislative authority.

IV. Jurisdiction over animal protection has traditionally been vested in the Federal Ministry for Agriculture (BMELV), which drafted the present draft legislation. However, it is in no way self-evident that an issue as comprehensive and highly detailed as the "Animal Protection-Laboratory Animal Regulation" should only be a matter for the BMELV, even though it is exclusively dedicated to the protection of animals used for scientific purposes. Indeed, it is worth considering placing the Federal Ministry for Research (BMBF) on an equal footing with the BMELV, or rather even comprehensively transferring to BMBF the authority to issue regulations in this area.

V. A decisive element in the implementation of animal experimentation in scientific practice is the existence of clear legal regulations and their uniform administration by the relevant authorities. Sections 7a and 8 of the draft legislation, which address this issue, may where appropriate be reformulated in more generally understandable terms and framed from a more general perspective, where possible by supplementation and streamlining. However, in the current version it is sufficiently clear that, in line with the existing legal position and its interpretation in light of the Constitution, decisive significance in determining the admissibility of a procedure is afforded to the scientifically-grounded presentation of the prerequisites for authorisation. The authorities are permitted to conduct a qualified plausibility review, but have no discretionary power of refusal. Nor may they impose their own assessments, for instance with regard to the ethical tenability of animal experimentation, in place of the scientifically-grounded presentation of the researcher. Anything else would result in an administrative veto power over science, which is precluded under the Basic Law and EU law in the same way that any state veto power over art is precluded.

Specific Recommendations

VI. Expertise: Setting training standards for specialist staff is recommended. Uniform federal certification should be introduced in conjunction with corresponding standardised training for physicians, veterinarians, scientists and biologists, and technical staff. Qualified specialists, including animal welfare officials, should not only include veterinarians but also suitably qualified scientists and biologists.

VII. Training aspects: Under the previous regulations, animal experimentation for basic and advanced training was only subject to the requirement of reporting, and not also approval. Consideration should be given to how this special arrangement may be retained in future, since such initiatives and treatments do not pursue any scientific experimental goal. In addition, sufficient capacity must be created in science and training to establish and continually improve staff members' required level of expertise.

VIII. Non-technical summary: Considering the high levels of specialisation within research, inferences may be easily drawn regarding individuals and locations and concrete experimental projects despite their anonymity. This particu-

larly applies if project goals including the number and type of animals used must be specified, as provided for under Section 41 of the draft regulation in relation to the publication of summaries. These rules do not sufficiently account for the legal positions of researchers, and unnecessarily fall short of the standard set in the EU Directive, Article 43 of which requires that intellectual property and confidential information within non-technical project summaries be safeguarded. An express requirement of this nature should not be absent from German law.

IX. Notification and approval procedure: Short turn-around times for animal experimentation applications are essential for research of high importance within a global competitive environment. The EU Directive provides for a processing period of 40 days, though it does not make provision for the possibility that time limits are not respected. Since the legal fiction (assumption of approval) previously provided for under German law has been removed, a sensitive gap within the regulations has emerged, which needs to be filled.

Notification requirements for projects and the scope of official examinations of projects that are only subject to a requirement of notification – in contrast to the requirements applicable to approval and the corresponding scope of the official examination – need to be relaxed. In addition, the period after which the experimental procedures may commence should remain limited to the previous term of ten working days.

X. Compliance costs: The enhancements to animal protection required under the amended legislation and the new regulation, particularly in relation to the keeping and use of laboratory animals and expanding the requirement of approval will result in high one-off and ongoing costs for the federal government, the federal states and the overall economy, which may amount to nine- or ten-figure sums. A general estimate of costs should be made, and the necessary funds be procured from the relevant budget.

2. Introduction

On 22 September 2010, Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes[1] (hereafter: the EU Directive) was adopted. This EU Directive essentially pursues the goals of harmonising the previous highly variable regulations within EU Member States and guaranteeing legal certainty throughout the EU. In substantive terms, the EU Directive seeks to strike a reasonable balance between animal protection and freedom of research, and also to enact conditions enabling the EU Member States to use the results of research involving animal experimentation, and in particular to exploit these results for protecting health and treating disease. As such, the EU Directive seeks to ensure that new pharmaceutical products and procedures may be developed within the EU in line with the highest scientific and animal protection standards. At the same time, along with the Europe 2020 Strategy[2], hindrances to research and innovation should be removed to enable the development of an economy based on knowledge and innovation.

The EU Directive must be transposed into national law within two years. Accordingly, in January 2012 the Federal Ministry for Food, Agriculture and Consumer Protection tabled draft legislation that included a revised Law on Animal Protection[3], as well as Laboratory Animal Regulation[4]. On 23 May 2012, the federal government approved draft legislation amending the Law on Animal Protection.

This proposed legislation is of major significance for life science research in Germany, and its implementation may achieve the stated goal of harmonisation by strengthening the internal market, as well as raising animal protection standards. On the other hand, inadequate implementation may turn into a significant barrier for biological and medical research, may jeopardise the achievement of the Europe 2020 Strategy goals, and may also represent a competitive disadvantage for research and innovation. Due to the planned expansion of the authorisation procedure into previously exempted areas, the number and scope of the necessary reporting and authorisation procedures for animal experimentation will increase significantly, which will also lead to an increase in animal experimentation numbers. The costs required to transpose the EU Directive for research and science – as well as for state-level administration

1 European Council, European Parliament (2010): Directive 2010/63/EU of the European Parliament and of the Council on the protection of animals used for scientific purposes (text with EEA relevance). Available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2010:276:0033:0079:en:PDF. Downloaded on 10 July 2011.

2 European Commission (2010): The Innovation Union flagship initiative. In: Europe 2020 – A Strategy for Smart, Sustainable and Inclusive Growth, p. 15. Available at: http://ec.europa.eu/eu2020/pdf/COMPLET%20%20DE%20SG-2010-80021-06-00-DE-TRA-00.pdf. Downloaded on 23 January 2012.

3 Federal Ministry for Food, Agriculture and Consumer Protection (2012): Tierschutzgesetz. Entwurf eines Dritten Gesetzes zur Änderung des Tierschutzgesetzes vom 09.01.2012 [Law on Animal Protection. Draft version of a Third Law Amending the Law on Animal Protection of 9 January 2012].

4 Federal Ministry for Food, Agriculture and Consumer Protection (2012): Entwurf einer Verordnung zur Umsetzung der Richtlinie 2010/63/EU des Europäischen Parlaments und des Rates vom 22. September 2010 zum Schutz der für wissenschaftliche Zwecke verwendeten Tiere vom 09.01.2012. [Draft version of a regulation to implement Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes of 9 January 2012].

– must be ascertained and coverage ensured.

In addition, a range of unclear if not contradictory formulations within the EU Directive, as well as in the presented draft legislation, provide cause for concern that new legal uncertainty may arise and that previous legal uncertainty may remain. According to past experience, such ambiguities would result in considerable problems related to the application for, approval and implementation of research projects – thereby turning into strong barriers and a serious locational handicap for biological and medical research in Germany.

The German National Academy of Sciences Leopoldina and the Union of the German Academies of Sciences and Humanities therefore consider it to be their task to represent both the significance of the use of animals within research and the scientific foundation for responsible use of laboratory animals in a well-balanced manner. Through their recommendations, these organisations wish to provide advice for the transposition of the EU Directive and its goals into national law, and thus facilitate the consideration of animal protection requirements and research in equal measure. Transposing the EU Directive should also provide impetus for providing enhanced legal certainty to researchers and reliable criteria to the authorities according to which the official authorisation procedures in Germany – which can differ significantly between regions – may be harmonised and transparent rules and procedures may be established.

3. Foundations for research involving animal experimentation

The necessity of and ethical justification for animal experimentation has been the object of intense discussion for some time, which in Germany has resulted in one of the world's strictest bodies of animal protection laws. There is a broad consensus that animal experimentation should be reduced to the minimum level necessary, but that it cannot be done away with in biological and medical research. There is an evident need for animal research, especially in the field of medical research, where significant progress within diagnostics and therapy are based on animal experimentation, since continuous therapeutic progress is expected and demanded by patients, and the State is obliged not only to ensure that such progress is not jeopardised, but also that it is actively promoted and facilitated.

There is a general consensus that animal experimentation should only be carried out where necessary and then under controlled conditions. A generally recognised principle in this area is the application of the 3Rs Principle, which stands for Replacement, Reduction and Refinement.[5] The 3Rs Principle is not only the basis for the legal framework governing animal experimentation, but also the scientific planning of tests. The responsibility of science for the 3Rs ongoing implementation is established by the "Basel Declaration" on experiments on animals.[6] In a manner similar to the 1964 "Declaration of Helsinki" on the ethical implementation of experiments on humans, the Basel Declaration calls for the responsible use of animal experimentation and has been signed by more than 1,000 scientists. Alternative procedures, for example the testing of pharmaceuticals on cell cultures, are used in many cases and enable animal testing to be *replaced*. A numerical *reduction* can be achieved, for example, through exact planning and improved statistical methods. At the same time, ways are being sought to reduce harm to laboratory animals by using non-invasive methods or more gently sedation techniques, or even by increasing the explanatory power of animal experimentation through particularly good diagnostics, and thus achieving *refinement*.

3.1 Ethical basis

A predominant view within the current ethical discussion on human dealings with animals is that humans are vested with the fundamentally moral right to use animals for their own ends, though this right becomes subject to limits where animals are significantly harmed by human actions or are killed without sufficient reason.[7] Under the established schema of normative positions relating to animal ethics, this position is classified as "pathocentric". On the other hand, a position is defined as "anthropocentric" if humans are also placed at the centre in relation to animal protection. A third relevant position here is the "ecocentric" or "biocentric" view, which assigns an ethical value to all living

5 Russell, W.M.S. & R.L. Burch (1959): The Principles of Humane Experimental Technique. Methuen, London.
Balls, M. & D.W. Straughan (1996): The three Rs of Russell & Burch and the testing of biological products. Dev. Biol. Stand. 86: 11–18.

6 Basel Declaration. Available at: http://www.basel-declaration.org. Downloaded on 23 January 2012.

7 Representative positions regarding the contemporary debate may be found in Wolf, U. (ed.): Texte zur Tierethik [Texts on Animal Ethics]. Reclam, Stuttgart: 2008.

organisms, including lower animals and plants. Whilst the extreme forms of these three positions are incompatible with one another, their more moderate forms may largely be regarded as reconcilable.[8]

According to the "anthropocentric" view, our conduct in relation to animals is to be assessed solely according to the measure of human interests, sentiments and feelings. For centuries this position, the most prominent representatives of which were Immanuel Kant and – from Christian moral theology – Thomas of Aquinas, has dominated our philosophical outlook. The essential tenet of Kant's position is that man alone has moral capacity, which results both in prerogatives and obligations. Animal protection is thus ultimately rooted in the self-respect of humans.

However, anthropocentrism was subject to a far-reaching and now generally accepted critique from a pathocentric perspective by Jeremy Bentham[9] and Arthur Schopenhauer.[10] According to Bentham, the decisive point is not whether animals think or speak like humans, but rather whether they can suffer like humans. All sentient beings must be ascribed with intrinsic value.

"Ecocentrism" or "biocentrism" in turn extend this intrinsic ethical value to all living beings, including lower animals and plants. Many supporters of this view even go so far as to ascribe an equally strong right to life and development to all non-human living beings. The most prominent example of this view is Albert Schweitzer's "The Ethics of Reverence for Life".[11] However, Schweitzer's view has the unacceptable consequence of not allowing for any differentiation between forms of living beings, and entirely disregards the extent of the subjective impact that humans' conduct has on animals.

An ethical system that is premised on the position that sentient animals have a moral status alongside humans occupies a compromise position between the two extremes mentioned above. This compromise ascribes sentient animals a lower moral status, which is indeed weaker than the status of humans, but is nonetheless significantly stronger than that of non-sentient animals and plants.

A pathocentric ethics of animals postulates the recognition of duties towards animals and places the avoidance of suffering at its core. However, it would be incorrect to assert that the avoidance of suffering *in its entirety*, also in relation to humans, is to be regarded as the most important of all measures. Overall, this approach may perhaps more appropriately be classified as a "patho-inclusive" ethics. This is not only reconcilable with the view that greater account should be taken of human interests than those of sentient animals, but also with the position that other human interests such as life and health, the acquisition of knowledge, and pleasure may be considered as justification for harming animals, alongside the avoidance of suffering for humans. Moreover, this view does not preclude the killing of animals, but rather requires that this occur, where possible, without pain or suffering.

Even though patho-inclusive ethics ascribe particular rights to animals, this system is not premised on the assumption that animals possess these rights inherently and independently of their allocation by humans. Rather, the undisputed

8 See further: Höffe, O. (2008): Anthropozentrisch – biozentrisch [Anthropocentric – biocentric]. In: Lexikon der Ethik [Lexicon of Ethics]. 7th edn., C.H. Beck, Munich: 21-22.

9 Bentham, J. (1789): Chapter 17: Of the Limits of the Penal Branch of Jurisprudence. In: Introduction to the principles of morals and legislation (Reprint 1828). Printed for W. Pickering, London, vol. 2: 232-277.

10 Schopenhauer, A. (1840): Grundlage der Moral [On the Basis of Morality], § 8. In: Die beiden Grundprobleme der Ethik [The Two Fundamental Problems of Ethics]. 2nd edn. 1860. Brockhaus, Leipzig: 160-168.

11 Schweitzer, A. (1923): Kulturphilosophie vol. 2: Kultur und Ethik [Culture and Ethics]. C.H. Beck, Munich.

position amongst animal ethicists of *epistemic* anthropocentrism – not to be confused with the *normative* anthropocentrism referred to above – rightly considers that only humans are capable of establishing, understanding and following moral obligations. Even though animals are the object of duties for humans, they are nonetheless reliant on the human efforts to provide meaning to their needs.

Supporters of an ethical duty to minimise animal suffering rely, on the one hand, on the fact that humans and animals are sentient beings, and on the other hand on the duties to refrain from causing suffering and to act to relieve the suffering of humans, which are recognised under all ethical systems. The principal argument for expanding these duties beyond the sphere of humans is that it is not evident why the corresponding duties should not in principle also apply to sentient animals. It is undisputed that animals are not moral creatures and cannot act as contracting parties capable of reaching agreement with humans on mutually existing rights and duties. However, this should not be a plausible reason for not ascribing animals a moral right – which may be weighed against other moral claims – to be spared as far as possible from suffering at the hands of humans. At least those animals in the care of humans, and those which have been specifically bred for human uses should be granted a moral claim to care and active relief from suffering.

This view, which predominates in animal ethics, also forms the basis for the German Law on Animal Protection. This means that animals are protected for their own sake – in contrast to older positions and arrangements that only protected animals if necessary to avoid causing offence to public decency or the supposed brutalisation of people. "For their own sake" does not mean that animals should also be regarded as being vested with individual rights. The basis for the German Law on Animal Protection is the "patho-inclusive" position that animal suffering must be regarded as a negative value, which may only be acceptable where the suffering caused is capable of protecting, securing or realising potential higher interests for humans and animals, whilst also being "indispensable" to that end. This view requires two forms of complex assessment and balancing operations to justify animal experimentation: a balancing of legal interests, and the determination of "indispensability". Both assessments are difficult, but not arbitrary. Regarding the comparison of these interests, human interests such as life and health generally have a stronger weight than the avoidance of suffering for animals. Moreover, there is also no certainty regarding animal suffering as there is for human suffering. Since animals do not cooperate when it comes to helping interpret their perceptions, there is a considerable likelihood of error both in the existence of suffering as well as its quality. Moreover, individual capacity for suffering will probably differ significantly between animals (as it does between humans). If there is great uncertainty regarding animal suffering, then the "certain" claims of humans should take priority. The "indispensability" of suffering means that no alternative methods are available to optimise the animal experimentation through *refinement* or to minimise the harm to animals with reference to the scientific, therapeutic, or any other purposes in accordance with the 3Rs Principle.

The criterion of capacity for suffering thus imposes limits on the experiments that may be performed on sentient animals, although it does not imply any categorical rejection of *harmful* animal experiments. On the contrary, the criterion in principle enables the harm to which the animals are exposed during the experiments to be weighed against the resulting positive benefit for humans. The criterion of capacity for suffering simultaneously

suggests that human obligations to minimise harmful animal experiments should essentially be measured with reference to the extent to which animals are capable of suffering based on their differing levels of neuronal development. Particular importance is ascribed to the capacity for self-perception of animals when classifying ethically grounded animal protection. Specific protection should be granted to animals that may be presumed to have a particularly large capacity due to their advanced stage of development, for example apes.

Moreover, it may be presumed that only part of the animal experiments carried out are harmful. A significant share of laboratory animals are kept in the laboratory and killed for their organs. In addition, there is also the category of "final animal experiments". Here, the animals are drugged prior to the start of the experiment and then killed at the end of the experiment, whilst still drugged – the goal being to save them from harmful painful experiences. The "patho-inclusive" ethics represented here does not have any principled objection to make against such experiments, provided that they are associated with advances in biological or medical knowledge that will benefit humans or that such advances are expected. This is because keeping animals in laboratories need not be classified as harmful as such, particularly for less cognitively developed animals. Indeed, laboratory animals often live longer, are more healthy and suffer less injuries from competitors or predators compared to those living in the wild.

The current German Law on Animal Protection marks out two boundaries with regard to the legal status of laboratory animals:

(1) a boundary between vertebrates and invertebrates, in that experiments on vertebrates generally require official authorisation, whilst experiments on highly-developed molluscs such as squid, which are similar to vertebrates in terms of neurophysiological sensitivity, are only subject to a requirement of notification;

(2) a border between these highly developed animals and all other invertebrates that – despite the emphatic commitment in Section 1 to animals as "fellow creatures" – are devoid of legal protection.

The law further requires that experiments on animals with higher neurophysiological sensitivity, particularly warm-blooded animals, should only be carried out if experiments on neurophysiologically less-developed animals are not sufficient for the purpose pursued.

The neurophysiological sensitivity is, however, less suited to demonstrating the level of capacity for suffering as a general criterion. To assess the capacity of animals to suffer, it is rather necessary to obtain a synopsis of neuronal, endocrynological and behavioural indicators according to the state of the art.

The special position that the EU Directive ascribes to non-human primates as a whole, or animals that are typically kept as pets, is questionable and is essentially justified by a reference to social perceptions and attitudes, and not with specialist arguments. However, the acceptance of mere attitudes and perceptions as adequate criteria for ascribing eligibility for protection is not straightforward. The way in which we deal with animals should be guided by the manner in which they are objectively affected, and not by our initial perceptions of them. Indeed, our attitudes are in many cases characterised by impressions such as perceived similarity with human children (young animals with child-like characteristics) or with ourselves (apes), although these impressions have little to say about animals' actual capacity for feeling and suffering. The special position adopted, for example in

relation to hamsters and guinea pigs in the previous German Law (section 9(8)) and in the draft regulation (section 28) is based on similar general perceptions, which have no scientific or ethical foundation. Perceptions are also culturally-dependent in a manner that is difficult to reconcile with the general validity claim of moral assessments.

3.2 Legal Considerations

3.2.1 Development of Animal Protection Law

1. The German law on animal protection has always been characterised by its particular strictness. The Reich Law on Animal Protection of 24 November 1933 imposed punishment for those who "unnecessarily distress or gravely mistreat an animal" (section 1). Section 5 of this law, which was based on years of preparatory work during the Weimar Republic, contains a general prohibition on "painful and harmful animal experimentation". The history of animal protection law in Germany after the Second World War involves the consistent heightening of the strictness of the relevant provisions. First and foremost, the admissibility of animal experiments for scientific purposes was subject to increasingly stringent restrictions.[12] The Law on Animal Protection of 24 July 1972 was still limited to replacing the old model of institution-wide approval with a requirement of specific approval for each individual range of experiments. The amendment of 12 August 1986 was intended, as is clear from the official grounds for its introduction, to tighten the legal rules within the field of animal experimentation. This primarily the framing of the purpose of experimentation in more restrictive terms, the mandatory appointment of animal protection officials, the establishment of animal protection boards, and the most important novelty, the introduction of the requirement of "ethical tenability" for the approval of experiments on vertebrates. Even stricter legislation was enacted twelve years later with the Law Amending the Law on Animal Protection of 25 May 1998: the expansion of animal protection to killing for scientific purposes, associated with a whole range of procedural and organisational requirements (including the duty to report and obtain approval), was applied to the implementation of animal experiments. More stringent and graded requirements were introduced, culminating in a general prohibition on animal experimentation for the development of all cosmetics, not only decorative cosmetics.[13]

2. It is undisputed that the current version of the Law on Animal Protection has as its central plank the concept of ethical animal protection. Section 1 of the Law on Animal Protection expresses this through the formulation of the phrase "animal as a fellow creature", whose "life and wellbeing are to be protected". This concept is elaborated within the commentaries on animal protection law to the effect that the law is based on the "basic conception of ethically aligned animal protection establishing the shared responsibility of humans for the living beings within their care".[14] Recognising an animal as a fellow creature results in it being protected for its own sake,[15] whereby its "inherent value"[16] must be acknowledged. Similarly, within primary EU law, Article 13 TFEU refers to the "welfare requirement of animals" as "sentient beings". However, this does not amount to the recognition of in-

12 For the following matters, see Lorz, A. & E. Metzger (2008): Tierschutzgesetz. Kommentar [Law on Animal Protection. Commentary]. 6th edn. Beck, Munich: Introduction para. 51ff.; Hirt, A., C. Maisack & J. Moritz (2007): Tierschutzgesetz. Kommentar [Law on Animal Protection. Commentary]. 2nd edn. Vahlen, Munich: Introduction, para 5 ff.

13 See the instructive Bundestag Paper 13/7015.

14 Lorz, A. & E. Metzger (2008): Tierschutzgesetz. Kommentar [Law on Animal Protection. Commentary]. 6th edn. Beck, Munich: Introduction, para 51.

15 Lorz, A. & E. Metzger (2008): Tierschutzgesetz. Kommentar [Law on Animal Protection. Commentary]. 6th edn. Beck, Munich: Introduction, para 60.

16 Hirt, A., C. Maisack & J. Moritz (2007): Tierschutzgesetz. Kommentar [Law on Animal Protection. Commentary]. 2nd edn. Vahlen, Munich: Introduction, para 22.

dividual rights of animals exercised on a fiduciary basis by third parties. Rather, it constitutes a minimum ethical level for responsible conduct with animals. Neither the Law on Animal Protection nor Article 20a of the Basic Law, which will be considered in greater detail below, establish any individual rights for animals. These regulations are rather provisions of objective law, which demand compliance by their addressees. Therefore, it would be too much to attempt, from the perspective of ethical animal protection, to discern a turn away from anthropocentric animal protection (i.e., protection focused on humans, their needs and their conceptions) in favour of an ecocentric or biocentric view.[17] This is because the anthropocentric reference proves, no differently from the position under environmental law, to be unavoidable simply due to the fact that animals are just as incapable of giving voice to their interests and legal claims as the environment is. It inevitably falls to the power of human interpretation and determination to ascertain the moral and legal status that is to be granted to animals.[18] The deeper reason for this also lies in the fact that the law can only relate to human conduct. Thus, inter alia, only an "anthropocentric construction of obligations" is meaningful.[19] Even those who argue in favour of an ecocentric or biocentric or ethical view of animal protection based on individual animal rights may essentially only bring their assessments as humans into play (and in a certain sense fix them in absolute terms), which are then granted to the environment, or respectively, to animals as independent rights.

3.2.2 Constitutional Law Considerations

1. In 2002 animal protection achieved constitutional status, which it does not have in any other EU Member State, through the introduction of the phrase "and animals" into Article 20a of the Basic Law. With this legislative change it was certain that the consideration of animal protection within constitutional law was both targeted and intended. However, this re-classification did not by any means have the result of establishing precedence for animal protection above all other interests. This is because the numerous other legal interests protected under constitutional law have not been deprived of value, downgraded, or even rendered inapplicable by the animal protection clause. In contrast, the animal protection now rooted in the Basic Law is to be weighed against other rules with constitutional status through practical concordance (balancing of competing and conflicting interests under the Basic Law). This is essentially undisputed within the literature and in the courts. Accordingly, the Federal Constitutional Court held as follows in its judgment of 12 October 2010 on the keeping of laying hens: "Article 20a of the Basic Law obliges the State authorities to protect animals [...]. With the adoption of animal protection into the Basic Law, the ethically-based animal protection, which was already covered by the Law on Animal Protection, should be enhanced [...]. Animal protection is to be taken into account within balancing decisions as an interest of constitutional standing – no differently from the environmental protection already elevated to a goal of the State under Article 20a of the Basic Law – and may be capable of justifying the reversion of other interests of constitutional standing – such as the limitation of basic rights – [...] although on the other hand it does not

17 The predominant view within the constitutional literature does not support such a stance. See e.g. Schulze-Fielitz, H. (2008): Kommentierung von Art. 20a GG [Commentary on Article 20a of the Basic Law]. In: Dreier, H. (ed.), Grundgesetz-Kommentar [Basic Law - Commentary]. vol. II, 2nd ed., Mohr Siebeck, Tübingen: p. 288-326 (para. 56); Kloepfer, M. (2011): Verfassungsrecht [Constitutional Law]. vol. I, Beck, Munich: section 12 paras. 62ff., and the references contained therein.

18 This also explains the broad spectrum of specific treatments of animals as well as their classification in relation to humans, which becomes clear from a comparative law and legal history perspective, and demonstrates the culturally-dependent status of animal protection.

19 Gärditz, K.F. (2011): Invasive Tierversuche zwischen Wissenschaftsethik und Wissenschaftsfreiheit [Invasive Animal Experimentation between Ethics of Science and Freedom of Science]. In: Wissenschaft und Ethik [Science and Ethics] (= Wissenschaftsrecht, supplement 21). Mohr Siebeck, Tübingen: p. 102.

necessarily take priority over competing interests of constitutional standing."[20]

2. Freedom of research and teaching, protected under Article 5(3) of the Basic Law, represents one such competing interest of central value under constitutional law. Already the fact that this basic right it not subject to a general reservation to the statutory realm, and hence is framed as a "basic right not subject to implementation through legislation", makes clear the high status that the constitutional legislator ascribed to freedom of research. However, the fact that freedom of research is a basic right not subject to implementation through legislation does not mean that it is not subject to limits. The limits to which freedom of research may be subject must in turn aim to protect legal interests of constitutional standing: according to the settled case law of the Federal Constitutional Court, only third parties and other legal interests vested with constitutional standing are capable of imposing limits, including limits on basic rights, without reservation.

Especially in relation to animal experimentation in the area of basic research, the freedom of each individual scientist to select the object of research and the methodology must be accounted for as an important interest under constitutional law. The decision to conduct animal experimentation falls within the area of the free choice of methodology. Science is a mainly inconclusive and open process involving the search for knowledge. The guarantee of scientific freedom thus benefits both individual scientists as well as research institutions, and protects a free space of scientific autonomy; the guarantee of freedom also includes precisely the autonomous determination of research goals and methods. This relates to the individual-subjective aspect of freedom of research. In addition, regarding its paramount significance for the continuing development of modern society in the social, economic, technical, and medical spheres, science, as a whole or as a system, forms the indispensable basis for civilising progress and social wellbeing. To summarise both functions, the Federal Constitutional Court has referred precisely in this sense to a "key function", "which free science [plays] both for the self-realisation of the individual as well as for overall social development."[21]

However, the central role and impact that freedom of science provides as the constitutional basis for animal experimentation is not the end of the matter. Indeed, for animal experiments that aim to improve the treatment of particular illnesses or develop new diagnostic methods or therapies within the area of human medicine, it is incumbent upon the State to protect the life and health of its citizens pursuant to both Article 2(2), as well as the basic law guarantee under Article 5(3). That Article 20a of the Basic Law may not be interpreted in a manner that would lead to a relativism regarding the existing duties to protect life and physical integrity has been expressly asserted within the literature.[22] The duty of care under constitutional law was asserted in even stronger terms in a recently published study on European animal protection law, which is significant for scientific animal experimentation where such experimentation is related to advances in medical knowledge for humans, or such advances are to be expected: "The defensive effect of the basic right of freedom of research in the area of biomedical research (basic and applied research) [is] enhanced by the effect of the duty of care established under the basic right to life and physical integrity (Article 2(2) of the Basic Law). Alongside

20 Federal Constitutional Court BVerfGE 127, 293 (328, para. 121).

21 Federal Constitutional Court, BVerfGE 35, 79 (114).

22 Schulze-Fielitz, H. (2008): Kommentierung von Art. 20a GG [Commentary on Article 20a of the Basic Law]. In: Dreier, H. (ed.), Grundgesetz-Kommentar [Basic Law - Commentary]. vol. II, 2nd ed., Mohr Siebeck, Tübingen: p. 288–326 (para. 89).

the scientific freedom of action for the researcher, the basic rights of other subjects are also affected, where they may expect to receive advantages from biomedical research in terms of the protection of their life or health." [23]

3. The protection under the Basic Law that is afforded to science and research is not subject to a blanket reservation of compatibility with the requirements of animal protection. On the contrary, against the backdrop of the principle of distribution within a free State governed by the rule of law, the fact that the exercise of basic law freedoms by the right-holder does not require any rational foundation or ethical justification, or a generally accepted setting of goals, is of central importance. The Basic Law does not postulate freedom of science within limits and subject to the requirements of animal protection, but rather provides for animal protection within the limits established by the constitutional order of basic rights. This is because the exercise of basic freedoms requires no justification, whilst such justification is required in order for them to be limited, even if this is based on legal interests of constitutional status. In addition, there are good grounds for supporting the view that "due to the division of the requirement of justification in accordance with the rule of law", individual freedom under the Basic Law enjoys "relative precedence over the abstract goal of the State, namely animal protection under Article 20a of the Basic Law".[24] Thus, the question can be laid to rest of whether an abstract and general precedence of guarantees to basic rights over mere assertions of the goals of the State may always be presumed.[25] The decisive consideration for the specific system of balancing is that whilst all of the legal interests referred to enjoy the same normative status in this regard since they are enshrined within the Basic Law, it does not by any means follow that they are to be afforded the same importance when balanced against one another. This is because whilst animal protection proclaims a goal of the State framed in general terms, freedom of research amounts to a classic individual defensive right against the State; the State's duty to protect the life and health of the population in turn relates solely to humans. Accordingly, there is an asymmetrical balancing scenario in which the rights and claims of humans are vested with a structurally greater interest than the concept of ethical animal protection. Within a constitutional system governed by the rule of law with human dignity at its heart (Article 1(1) of the Basic Law), this predominance of human legal interests is set in stone.

4. The corresponding conflict of goals between freedom of research and animal protection are not settled in favour of animal protection by Article 20a of the Basic Law. Here, as in comparable constellations, striking a specific balance between countervailing interests through a reasonable settlement is in the first instance a matter for the parliamentary legislature.

23 Cornils, M. (2011): Reform des europäischen Tierversuchsrechts [Reform of European Animal Protection Law]. Zur Unions- und Verfassungsrechtmäßigkeit der Richtlinie 2010/63 des Europäischen Parlaments und des Rates zum Schutz der für wissenschaftliche Zwecke verwendeten Tiere. [On the compatibility with EU and constitutional law of Directive 2010/63 of the European Parliament and of the Council on the protection of animals used for scientific purposes] LIT Verlag, Berlin: p. 114f.

24 Gärditz, K.F. (2011): Invasive Tierversuche zwischen Wissenschaftsethik und Wissenschaftsfreiheit [Invasive Animal Experimentation between Ethics of Science and Freedom of Science]. In: Wissenschaft und Ethik [Science and Ethics] (= Wissenschaftsrecht, supplement 21). Mohr Siebeck, Tübingen: p. 112; for a clear and concise statement, see DVBl. 2010, p. 1049: "Individual freedom under constitutional law enjoys [...] a position of relative predominance over an abstract goal of the State"; see also Spranger, T.M. (2000): Auswirkungen einer Staatszielbestimmung „Tierschutz" auf die Forschungs- und Wissenschaftsfreiheit. [Implications of the determination of "animal protection" as a goal of the State on freedom of research and science.] In: Zeitschrift für Rechtspolitik: p. 285ff. and p. 287f.

25 For further discussions of this issue see Cornils, M. (2011): Reform des europäischen Tierversuchsrechts [Reform of European Animal Protection Law]. Zur Unions- und Verfassungsrechtmäßigkeit der Richtlinie 2010/63 des Europäischen Parlaments und des Rates zum Schutz der für wissenschaftliche Zwecke verwendeten Tiere. [On the compatibility with EU and constitutional law of Directive 2010/63 of the European Parliament and of the Council on the protection of animals used for scientific purposes] LIT Verlag, Berlin: p. 84ff.

This bodies' necessary task of concretisation cannot and may not be passed over by direct action by the courts or the executive. On the grounds of democratic legitimation and precision as required by the rule of law, clear and reliable statutory rules governing the licensing of animal experimentation are not only desirable but also required under constitutional law.

5. The normative framework within which the concrete decision on animal experimentation is to be made is established under the current state of the law, particularly in sections 7 and 8 of the Law on Animal Protection. According to the predominant and correct position within the literature and case law, these provisions ensure that a balance is struck between freedom of research on the one hand, and animal protection on the other. This is assured through a carefully calibrated network of requirements to state the reasons, proportionality examinations and entitlements to carry out such controls.[26]

Without delving further into the legal details, the balance between freedom of research and animal protection provided for under the relevant statutory provisions may be expressed by the requirement that researchers are subject to particular disclosure requirements, whilst at the same time the approval authorities are granted particular rights of examination, which may in fact be reduced to a "qualified plausibility review". Section 7(3) of the Law on the Protection of Animals requires that applicants, i.e. researchers in particular, disclose the scientific significance of the experiment's purpose. In this respect the applicant is subject to a particular duty of disclosure, which must be complied with. The authorities in turn are entitled to examine the tenability of the scientific basis for the application, and are entitled to carry out the "qualified plausibility review" referred to above, which in concrete terms means that ambiguities and misjudgements, materially incorrect statements or the evident departure from existing standards of scientific research will result in the application's refusal. However, as the Federal Constitutional Court held many years ago (and which has not been changed by the introduction of new text into Article 20a of the Basic Law), the authorities may not "replace their assessment of the significance of the purpose of the experimentation for the assessment of the applicant scientists".[27] Ultimately, the researcher's autonomous capacity of assessment will take precedence over an approval authorities' "veto power over science", which has no foundation in constitutional law. The scope of the freedom protected under constitutional law cannot and may not depend on the ultimately subjective assessment of an official or an animal protection expert regarding the extent of ethical tenability.
These guidelines have been fleshed out in greater detail in the administrative courts.[28] Thus, Section 7(3)(i) of the Law on Animal Protection, according to which the "ethical tenability" of the animal experimentation is a prerequisite for approval, must be interpreted to the effect "that approval must be granted where the prerequisites for approval laid down thereunder are met. The granting of additional discretion to the competent authorities would not be compatible with the freedom of research guaranteed under the Basic Law. Thus, freedom of research would ultimately be at the mercy of the authorities." This basic assertion is largely

26 Löwer, W. (2006): Tierversuche im Verfassungs- und Verwaltungsrecht. Zugleich ein Beitrag zum bremischen Staatsrecht [Animal Testing in Constitutional and Administrative Law. Also a contribution to the State law of Bremen] (= Wissenschaftsrecht, supplement 16). Mohr Siebeck, Tübingen: p. 47ff. and p. 55ff.

Gärditz, K.F. (2011): Invasive Tierversuche zwischen Wissenschaftsethik und Wissenschaftsfreiheit [Invasive Animal Experimentation between Ethics of Science and Freedom of Science]. In: Wissenschaft und Ethik [Science and Ethics] (= Wissenschaftsrecht, supplement 21). Mohr Siebeck, Tübingen: p. 115ff.

27 Federal Constitutional Court, BVerfGE, 1st Chamber of the First Senate, NVwZ 1994, S. 894f.

28 For greater detail, including references to further judgments and literature, see: Bremen Administrative Court, DVBl. 2010, p. 1044.

endorsed – though not without exception – within the scientific literature.[29] Ethical tenability thus does not relate to the tenability of animal experimentation as such, but rather requires an appropriateness test in which the pain, suffering or harm to laboratory animals is weighed against the goals of the experiment and the scientific knowledge it is expected to reveal. However, the approval authorities are granted no margin for manoeuvre or discretion when assessing the experiment's purpose. The decisive issue is rather the assessment of the scientist, as they are the sole party entitled to carry out the "qualified plausibility review". The authorities are accordingly not entitled to substitute their own assessment for that of the applicant scientist, but may rather only review its plausibility. This follows from the wording of section 8(2) of the Law on Animal Protection, according to which approval is to be granted if the existence of the substantive prerequisites set out in Section 7 have been "demonstrated in a scientifically well-founded manner". The authorities will therefore not examine independently and using their own powers of assessment whether the prerequisites of section 7 have been met, particularly including the requirement of "ethical tenability", but rather only whether the applicant has furnished scientifically grounded indications that the prerequisites have been met.[30] Also, section 8(1) of the draft amendment to the Law on Animal Protection should be interpreted in accordance with this understanding.

6. These principles are also relevant, above all, in the area of basic research. Animal experimentation directed at achieving basic scientific knowledge may not be prohibited on the grounds that its actual usability is still unclear. This is because the open-ended nature of results and the lack of a specific use are two of the hallmarks of basic research, the constitutional law protection for which is not weaker than that of applied research. The Bremen Administrative Court has held in this regard[31] that: "This decision by the legislature (co-existence with equal value of the legitimate experimentation goals of basic research and applied research) must be taken into account when applying the law in the assessment of benefits and harm. It may not be undermined by the denial of specific plausibility to basic research [...] within the balancing decision. [...] Basic scientific research is thus ascribed an intrinsic cultural value, [and] the resulting specific reduction in suffering expected for humans is not in principle taken into consideration, as it is generally not possible to assess them in this area. Whilst on this view the causing and avoidance of suffering must be weighed with applied research on laboratory animals, such a consideration is in principle superfluous in the area of basic research, at least where the basic research is of high scientific quality and promises a significant advance in knowledge." Furthermore (p. 1048): "The fact that the knowledge obtained in relation to basic research lacks any specific use or specific plausibility may not be deemed to be relevant for the purposes of the decision on the balancing of interests. [...] Otherwise, requirements would be placed on basic research which

29 Löwer, W. (2006): Tierversuche im Verfassungs- und Verwaltungsrecht. Zugleich ein Beitrag zum bremischen Staatsrecht [Animal Testing in Constitutional and Administrative Law. Also a contribution to the State law of Bremen] (= Wissenschaftsrecht, supplement 16). Mohr Siebeck, Tübingen: p. 71ff., along with a discussion of other views.

Gärditz, K.F. (2011): Invasive Tierversuche zwischen Wissenschaftsethik und Wissenschaftsfreiheit. [Invasive Animal Experimentation between Ethics of Science and Freedom of Science] In: Wissenschaft und Ethik [Science and Ethics] (= Wissenschaftsrecht, supplement 21) Mohr Siebeck, Tübingen: p. 116ff., along with a discussion of other views.

30 See Löwer, W. (2006): Tierversuche im Verfassungs- und Verwaltungsrecht. Zugleich ein Beitrag zum bremischen Staatsrecht [Animal Testing in Constitutional and Administrative Law. Also a contribution to the State law of Bremen] (= Wissenschaftsrecht, supplement 16). Mohr Siebeck, Tübingen: p. 75ff; Gärditz, K.F. (2011): Invasive Tierversuche zwischen Wissenschaftsethik und Wissenschaftsfreiheit. [Invasive Animal Experimentation between Ethics of Science and Freedom of Science] In: Wissenschaft und Ethik [Science and Ethics] (= Wissenschaftsrecht, supplement 21) Mohr Siebeck, Tübingen: p. 116ff.

31 DVBl. 2010, p. 1044 and p. 1046.

it would not as a rule be capable of satisfying and which would lead to a situation in which the co-existence of equal terms, sanctioned by the legislators, of acquired abstract knowledge on the one hand and the specific usage of applied research on the other hand would be undermined upon application."

In other words, the fact that a lacking or insufficiently clearly stated social "benefit" of animal experimentation in the area of basic research is not capable of justifying a denial of approval is clear from the consideration that basic research is, by definition, foreign to such a readily-presentable calculation of benefits.

3.2.3 EU Law

When transposing the EU Directive on animal protection into German law, the federal legislature must first implement its requirements; however, particularly where the EU Directive leaves margin for manoeuvre, the principles laid down in the Basic Law must be fully implemented. Due to the generally recognised precedence of EU law – other than in extremely exceptional cases – only in the event of a conflict would the EU Directive be enforced, even notwithstanding the constitutional law of the Federal Republic of Germany. However, in view of the present EU Directive, such a conflict would be purely hypothetical. This is first because the rules laid down in the foundations of EU law provide for structurally identical assessments and balancing operations as those set out in the Basic Law (see section 1). Secondly, since the EU Directive is to be interpreted in a manner compatible with primary law in light of the Treaty on the Functioning of the European Union (TFEU) and the Charter of Fundamental Rights (CFR), conflicts regarding matters of principle between the legal position set out under constitutional law in Germany and the provisions of the EU directive will not arise (see section 2).

1. Animal protection is regulated under Article 13 TFEU through the "horizontal clause". However, horizontal clauses,[32] which are already used in environmental and consumer protection, are not vested with any undisputed overarching position compared to legal rights and interests.[33] Strikingly, compared to other horizontal clauses, animal protection is formulated in even more restrained terms, since Article 13 TFEU merely uses the formula "pay full regard to", whilst for instance environmental protection requirements must be "integrated" under Article 11 TFEU. All the same, regardless of whether particular significance is ascribed to this difference, it is nonetheless clear that animal protection has just as little pre-eminent significance with priority over all other legal interests and concerns under European primary law as it has under German constitutional law.

However, similar to the Basic Law, European primary law also guarantees individual freedom of research. It is therefore an open question whether a basic right of scientific freedom has always been available under the constitutional traditions common to the Member States. However, the position has been clearly formulated under Article 13 CFR: "The arts and scientific research shall be free of constraint. Academic freedom shall be respected." Insofar as any remaining space is available, the guarantees laid down in the European Convention on Human

32 Article 13 TFEU provides that: "In formulating and implementing the Union's agriculture, fisheries, transport, internal market, research and technological development and space policies, the Union and the Member States shall, since animals are sentient beings, pay full regard to the welfare requirements of animals, while respecting the legislative or administrative provisions and customs of the Member States relating in particular to religious rites, cultural traditions and regional heritage."

33 On this and the following, see Cornils, M. (2011): Reform des europäischen Tierversuchsrechts [Reform of European Animal Protection Law]. Zur Unions- und Verfassungsrechtmäßigkeit der Richtlinie 2010/63 des Europäischen Parlaments und des Rates zum Schutz der für wissenschaftliche Zwecke verwendeten Tiere. [On the compatibility with EU and constitutional law of Directive 2010/63 of the European Parliament and of the Council on the protection of animals used for scientific purposes] LIT Verlag, Berlin: p. 42ff., containing further references.

Rights (ECHR) should be considered; although scientific freedom is not expressly regulated thereunder, it may be deemed to enjoy joint protection under Article 10 ECHR (freedom of expression).

Thirdly and finally, the protection of life and health is afforded a high status under primary law. This is clear in purely quantitative terms from the large number of relevant provisions in the TFEU (Articles 9 and 168) and the EU Charter of Fundamental Rights (Articles 2 and 3), as well as the ECHR (Article 2). Since the notion of a duty of protection within fundamental rights is also familiar in EU law and the case law of the European Court of Justice (ECJ), this results in corresponding duties in the enactment of EU law. Specifically, this means that when enacting legislation that addresses animal protection, EU lawmakers are required to carefully consider the duty to protect the life and health of its citizens, which is grounded in the primary law of the EU. The ECJ has always ascribed high status to the protection of health in its case law. In particular, the stringent judgments on the legality of tobacco advertising bans show that invasive infringements of basic economic rights may be acceptable for the benefit of protecting public health. Article 114(3) TFEU should also be given particular emphasis in this regard.[34] According to this provision, a high level of protection is to be presumed in the area of health protection, and all new developments based on scientific results are to be considered. It may be plausibly argued that it would run contrary to this requirement to prohibit animal experimentation with the goal of acquiring new knowledge for human medicine. Reference has thus been made, with good reason, to a "relative priority of protection of health in assessments with the policy goal of environmental protection".[35]

2. Against the abovementioned backdrop, a central consequence for an interpretation of the EU Directive that conforms with primary law is that a far-reaching roll-back of freedom of research and the resulting disregard to the protection of public health must be subject to strict limits. This may be shown through two examples.

a) The freedom of research enshrined in the primary law of the EU precludes the operation of a "harm-benefit analysis" within basic research in the same manner as for applied research animal experiments. This is because such a rule would either require the impossible or enable the authorities to impose a blanket refusal on all applications for animal experimentations directed at basic research on the grounds that it lacks any "use". Whoever signs up to freedom of research, as the EU has done through Article 13 CFR, must also endorse specifically basic research. This is also expressly referred to in Article 5(a) of the Directive. Accordingly, it would be a contradiction in terms were the interpretation of the approval requirements to result, in an entirely utilitarian manner, in the removal of the basis for the expressly recognised basic research.

b) Article 38 of the EU Directive provides for individual project evaluation by the authorities. On the other hand, the EU Directive does not specify on which basis the approval authorities are to conduct the project assessment falling to them. This by no means precludes the possibility that when doing so – as currently occurs

34 Article 114(3) TFEU provides that: "The Commission, in its proposals envisaged in paragraph 1 concerning health, safety, environmental protection and consumer protection, will take as a base a high level of protection, taking account in particular of any new development based on scientific facts. Within their respective powers, the European Parliament and the Council will also seek to achieve this objective."

35 Cornils, M. (2011): Reform des europäischen Tierversuchsrechts [Reform of European Animal Protection Law]. Zur Unions- und Verfassungsrechtmäßigkeit der Richtlinie 2010/63 des Europäischen Parlaments und des Rates zum Schutz der für wissenschaftliche Zwecke verwendeten Tiere. [On the compatibility with EU and constitutional law of Directive 2010/63 of the European Parliament and of the Council on the protection of animals used for scientific purposes] LIT Verlag, Berlin: p. 72.

under German practice – the documents presented by the applicant and their assessment of the scientific relevance of the animal experimentation should play a decisive role. The requirement for a review of the ethical tenability of the experimentation is thus "open to different institutional arrangements".[36] In Germany, based on constitutional law, this requirement must continue to be subject to the qualified plausibility review.

36 Gärditz, K.F. (2011): Invasive Tierversuche zwischen Wissenschaftsethik und Wissenschaftsfreiheit. [Invasive Animal Experimentation between Ethics of Science and Freedom of Science] In: Wissenschaft und Ethik [Science and Ethics] (= Wissenschaftsrecht, supplement 21) Mohr Siebeck, Tübingen: p. 127.

4. Areas of animal experimentation

At present, approximately 2.9 million animals are used for research in Germany (*Table 1*). Of this number, around 2.1 million animals are used directly in animal experimentation, whilst around 0.8 million animals are killed to procure their tissue, or for the application of cell cultures.[37] Around 48 percent of animal experiments involve basic research, along with targeted translational research that investigates or treats illnesses. Approximately 46 percent of all animal experiments occur for the purpose of the development, quality control and safety control of pharmaceuticals and medicinal products. A significant share of these animal experiments is required under legislation or is carried out in accordance with statutory provisions, for example the Law on Pharmaceuticals. The remaining six percent of all animal experiments is carried out for basic and advanced training, the diagnosis of disease, the examination of pesticides, and other purposes. This breakdown shows that, alongside their relevance for research, the results of animal experiments are directly significant for the health, quality of life, and safety of humans.

Compared to the 2.9 million laboratory animals used in 2010, more than 740 million animals were killed for food purposes[38], whilst 4.8 million animals were killed during the 2009/2010 hunting season.[39] The animals used in Germany for experimental purposes thus represent less than 0.4 percent of the total number of animals killed in Germany.

Table 1: Use of animals in Germany
Figures in millions[40]

Total number of laboratory animals (2010)		2,9
of which	mice	2,0
	rats	0,4
	rabbits	0,09
	guinea pigs	0,03
	pigs	0,013
	monkeys	0,002

Animal experiments are conducted for various purposes and are used to investigate complex phenomena that cannot be addressed using simpler methods. For example, it is only possible to discover whether a pharmaceutical lowers blood pressure by using it on a living organism. In these areas, animal experiments will continue to be essential for as long as there are no safe, equivalent and, as appropriate, permitted alternatives. In many cases these experiments represent a significant building block for current and

37 Federal Ministry for Food, Agriculture and Consumer Protection (2012): Tierversuchszahlen des Jahres 2010. Statistik des Bundesministeriums für Ernährung, Landwirtschaft und Verbraucherschutz [Animal experimentation statistics for the year 2010. Statistics of the Federal Ministry for Food, Agriculture and Consumer Protection]. Available at: http://www.bmelv.de/SharedDocs/Standardartikel/Landwirtschaft/Tier/Tierschutz/ Versuchstierzahlen2010.html. Downloaded on 23 January 2012.

38 Federal Office for Statistics (2011): Statistisches Jahrbuch 2011 für die Bundesrepublik Deutschland mit „Internationalen Übersichten“ [2011 Statistical Yearbook for the Federal Republic of Germany with “International Overviews”]. Federal Office for Statistics, Wiesbaden.

39 German Hunting Association (2012): Handbuch 2012, Jagdstrecken der Bundesrepublik Deutschland [2012 Handbook, Hunting Routes in the Federal Republic of Germany]. Hunting Season 1 April 2009 31 March 2010. Available at: http://medienjagd.test.newsroom.de/201011_ jahresjagdstrecke2.pdf. Downloaded on 23 January 2012.

40 Federal Ministry for Food, Agriculture and Consumer Protection (2012): Tierversuchszahlen des Jahres 2010. Statistik des Bundesministeriums für Ernährung, Landwirtschaft und Verbraucherschutz [Animal experimentation statistics for the year 2010. Statistics of the Federal Ministry for Food, Agriculture and Consumer Protection]. Available at: http://www.bmelv.de/SharedDocs/Standardartikel/Landwirtschaft/Tier/Tierschutz/ Versuchstierzahlen2010.html. Downloaded on 23 January 2012.

future medical progress, or form the basis for our knowledge regarding the functioning, diseases, reproduction and lifestyles of animals.

The following paragraphs will provide several examples of animal experiments. Here, it must once again be stressed that during all such experiments measures are adopted to minimise both the number of and the harm caused to the animals involved in the experiment according to the 3Rs Principle (see p. 14).

4.1 Basic Research

Basic research involves animal experimentation in practically all areas of the natural sciences in which the complex functions of living organisms are investigated. This may be illustrated by two examples:

The first example relates to hibernation, which is engaged in by many mammals. Hibernation results in a fall in body temperature to values close to freezing, whereby all bodily functions are extremely slowed down. It was initially thought that hibernation involved the discontinuation of temperature regulation in these animals, which was sparked by the cold and a lack of nutrition. However, animal experimentation has shown that hibernation is a precisely regulated state. This became clear through the observation that hibernating creatures wake up every 10 to 14 days from their coldest state, remain awake for one day, and then spontaneously fall back into the quasi-paralysis known as "torpor". The heartbeat in this state is significantly slowed, breathing may stop for one hour or longer, and the body's energy use sinks to one-hundredth of its ordinary requirement. For a long time this was considered to be a consequence of low body temperature, although researchers were later able to demonstrate that the mechanism was precisely the opposite: the metabolic rate is actively blocked, with the consequence that body temperature and other physiological performance fall. This was established through experiments in which dormice and marmots were kept in air-conditioned cages for months during hibernation, and breathing and body temperature were measured along with an ECG at different temperatures. A new metabolic regulator was thereby discovered for mammals, through which they were able to switch over from normal usage to the pilot-light mode.[41]

Although these kinds of animal experiments relate to research that obtains knowledge without a specific purpose, various medical applications – which were at first surprising – did emerge. Switching one's metabolism to the "pilot-light mode" could be beneficial for the treatment of seriously injured people, containing the consequences of a stroke or heart attack, or in transplant medicine to reduce the needs of the injured or transplanted organ. An improved knowledge of metabolic processes during hibernation can also contribute to understanding neuro-degenerative diseases. Degenerative processes are initiated in the brain during hibernation, synaptic contacts are shut down and – in a manner similar to the start of dementia – specific bio-chemical changes may be observed (for example the hyperphosphorylation of the tau protein). During the awakening periods every 10 to 14 days, these losses are rectified by hibernating animals within one day.[42] It would be extremely useful for medical research into neuro-degenerative diseases to understand how these repair processes operate.

A second example involves the capacity of humans and animals to locate sound sources. The localisation of sound is an important element for orientation,

41 Heldmaier, G., S. Ortmann & R. Elvert (2004): Natural hypometabolism during hibernation and daily torpor in mammals. Respir. Physiol. Neurobiol. 141: 317–329.

42 Arendt, T. (2004): Neurodegeneration and plasticity. Int. J. Dev. Neurosci. 22: 507-514.

and may be used to avoid sound sources (e.g. when fleeing from a predator), to attack sound sources (for predators), or to communicate with others (e.g. during courtship). Sound localisation also plays an important role in oral communication between people. For example, by localising sound we are able to focus on one speaker from a crowd and thus better understand them (the "Cocktail Party Effect"). The barn owl is a specialist in sound localisation, and may locate its prey precisely using only its hearing; this owl has gained many capabilities and biological characteristics through evolution that enable us to understand basic problems and natural solutions in the localisation of sound. By observing the reactions of nerve cells and the behaviour of barn owls to acoustic stimulation, it has been possible to decipher the basic mechanisms of sound localisation and the neuronal network that are used for the "Cocktail Party Effect".[43] These originally pure basic research experiments have then resulted in practical applications, e.g. the improvement of hearing aids.[44]

4.2 Research for the Benefit of Animals

The knowledge obtained from animal testing can also frequently be used for the benefit of animals, particularly research into animal diseases. An example of this is the "white nose syndrome" in bats, which was observed in North America for the first time in 2006. This syndrome is caused by a fungus epidemic responsible for unparalleled mass deaths: since the outbreak of the disease millions of bats have died in the USA during hibernation.[45] The responsible fungus, *Geomyces destructans*, was also discovered in European bats, which to date appear to have survived the infection essentially unharmed.[46] The mechanisms underlying the infection are still largely unclear. Without this kind of knowledge, it is not possible to reliably assess the danger of a similar mass death in Europe, nor can measures be adopted to protect against a potential epidemic.[47] To understand the immunological basis for the infection and the mechanisms by which it spreads, it is necessary to infect bats with the fungus on an experimental basis and investigate their immune responses. Since this involves complex processes within the organism as a whole, the animal experimentation cannot be replaced with alternative procedures on isolated organs or tissue. Rather, animal experiments are essential to investigate this disease, to develop suitable countermeasures, and to prevent a potentially imminent mass death of bats in the wild.

A further area in which animal experiments are beneficial for animals is the development and optimisation of methods within veterinary medicine, animal breeding, assisted reproduction and livestock management. For example, animal experimentation is essential for reducing animals' stress levels while taking blood samples and other treatments; this involves testing new procedures and investigating the animals' responses.[48] New methods can only be put into practice once such ex-

43 Wagner, H., A. Asadollahi, P. Bremen, F. Endler, K. Vonderschen & M. von Campenhausen (2007): Distribution of interaural time difference in the barn owl's inferior colliculus in the low- and high-frequency ranges. J. Neurosci. 27: 4191-4200.

44 Kollmeier, B. (2002): Cocktail-Partys und Hörgeräte: Biophysik des Gehörs. [Cocktail Parties and Hearing Aids: the biophysics of hearing] Physik Journal 1 (4): 39-45.

45 Frick, W.F., J.F. Pollock, A.C. Hicks, K.E. Langwig, D.S. Reynolds, G.G. Turner, C.N. Butchkoski & T.H. Kunz (2010): An emerging disease causes regional population collapse of a common North American bat species. Science 328: 679-682.

46 Wibbelt, G., A. Kurth, D. Hellmann, M. Weishaar, A. Barlow, M. Veith, J. Pruger, T. Gorfol, L. Grosche, F. Bontadina, U. Zophel, H.-P. Seidl, P.M Cryan & D.S. Blehert (2010): White-Nose Syndrome fungus (Geomyces destructans) in bats, Europe. Emerg. Infec. Dis. 16: 1237-1242.

47 Puechmaille, S.J., W.F. Frick, T.H. Kunz, P.A. Racey, C.C. Voigt, G. Wibbelt & E.C. Teeling (2011): White Nose Syndrome: An emerging disease threat to temperate zone bats. Trends Ecol. Evol. 26: 570-576.

48 Hofer, H. & M.L. East (2012): Stress and immunosuppression as factors in the decline and extinction of wildlife populations: the concepts, the evidence and the challenges. In: Aguirre, A.A., P. Daszak & R.S. Ostfeld (eds.): Conservation medicine: applied cases of ecological health. Oxford University Press, New York: 82-107.

periments have been carried out successfully and in a scientifically well-founded manner. Many animals benefit from less invasive veterinary procedures.[49] Moreover, new methods are being constantly developed for the management of livestock and wildlife breeding and releasing programmes, which require research that involves animal experimentation.[50] For example, in many African countries excessive growth in elephant populations, which are restricted to geographically limited areas, causes significant problems. Many animals are killed or wounded in conflicts with humans, and in many places the capacities of existing reserves are not sufficient for the size of the populations. These situations could be eased by the development and use of contraception methods for elephants[51], which resulted in a significant improvement of the living conditions of elephant populations in the wild. Where feasible, alternative and supplementary methods are used when developing methodology and assessing the results' success. However, the efficacy and possible implications of new procedures cannot be clarified without carrying out experiments on living animals.[52]

4.3 Research for the Benefit of Humans

A significant share of animal testing occurs in relation to medical research carried out to enable and improve diagnoses and therapies of untreatable or not sufficiently treatable diseases. According to Principle 12 of the Declaration of Helsinki on "Ethical Principles for Medical Research Involving Human Subjects"[53], "Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected." This Principle states that animal experiments must always be conducted prior to research in humans if such experiments are necessary to derive hypotheses, or if they may be expected to improve safety for test participants or patients. Such experiments are thus intended to ensure that patients are not exposed to an avoidable higher risk.

4.3.1 Infection Research and the Development of Vaccines

Animal experimentation is necessary to analyse complex biological reactions and processes that only occur within a complete organism. This includes research into the emergence of numerous human infectious diseases, as well as the development of vaccines. An example of such complex processes is the immunological reaction to pathogens. Immune cells may at present only be taken from a living organism, whether human or animal, and new vaccines against microbial pathogens must be tested on animals prior to use on humans. Moreover, to clarify how infectious diseases arise and develop it is necessary to carry out animal experimentation (incl. studies on nonhuman primates) for pathogens specific to primates and humans.

Vaccines against viruses and bacteria are one of the major medical achievements of the last century, and their development has enabled the classical

49 Voigt, C.C., M. Faßbender, M. Dehnhard, K. Jewgenow, G. Wibbelt, H. Hofer & G.A. Schaub (2004): Validation of a minimally invasive blood sampling technique for hormonal analysis in domestic rabbits. Gen. Comp. Endocr. 135: 100-107.

50 Göritz, F., M. Quest, T.B. Hildebrandt, H.H.D. Meyer, L. Kolter & K. Jewgenow (2001): Antiprogestins – a new approach to control reproduction in captive bears. J. Reprod. Fert. (Suppl.) 57: 249-254.

51 Fayrer-Hosken, R.A., D. Grobler, J.J. Van Altena, H.J. Bertschinger & J.F. Kirkpatrick (2000): Immunocontraception of African elephants. Nature 407: 149.

52 Jewgenow, K., M. Dehnhard, T.B. Hildebrandt & F. Göritz (2006): Contraception for population control in exotic carnivores. Theriogenology 66: 1525-1529.

53 World Medical Association (WMA) (2008): Declaration of Helsinki Ethical Principles for Medical Research Involving Human Subjects. Available at: http://www.bundesaerztekammer.de/downloads/ DeklHelsinki2008.pdf. Downloaded on 23 January 2012.

infectious child diseases to be combated through vaccination. Based on animal models, these infections were entirely eradicated (e.g. smallpox) or significantly reduced and almost eradicated (e.g. polio, measles and rubella). Diseases that previously afflicted hundreds of thousands of people and which could be deadly or cause serious damage have thus been largely eradicated in many countries. However, their eradication has also resulted in their dangerousness being largely forgotten.

Vaccinations are one of the most significant achievements of medical science; their development was based on experiments on small animals (e.g. rodents), along with experiments on non-human primates. Above all, the development and testing of the polio vaccine was mainly based on results obtained from experiments on primates. Such tests are also currently required by licensing authorities prior to the licensing of vaccines intended to protect against pathogens that affect the nervous system.

The so-called "Monkey Neurovirulence Test" (MNVT) is the standard test used to ascertain neuro-toxicity, since the central nervous system of non-human primates is closest to that of humans with regard to its biological vulnerability.[54]

Thanks to advances in the clarification and analysis of new pathogens, intensive work is currently being carried out to develop vaccines against further infections such as HIV, Hepatitis C or Malaria. Where possible, parts of these developments are carried out using small laboratory animals, and attempts are increasingly being made to replace primates with e.g., genetically modified mice (see below). However, investigations on non-human primates will be necessary for the foreseeable future to demonstrate the efficacy and innocuousness of such vaccines before they are deployed against the most serious human infectious diseases. This particularly applies for pathogens and diseases that are specific to primates – including Ebola, Dengue Fever and HIV/AIDS.[55]

4.3.2 Development of Pharmaceuticals

The development of new therapeutic procedures, particularly new pharmaceuticals, occurs as a rule from knowledge obtained through basic research – which is occasionally targeted, but often gained by chance – on hypotheses regarding new therapy options, which may then be pursued further in a systematic manner. Animal experimentation is thus of central significance during pre-clinical efficacy trials, as well as in the examination of innocuousness. The necessary steps and procedures are laid down in the Law on Pharmaceuticals and the corresponding European regulations. Compliance with these regulations is monitored by the competent authorities, including, first and foremost, the German Federal Institute for Drugs and Medical Devices (Bundesamt für Arzneimittel und Medizinprodukte, BfArM), the European Medicines Agency (EMA), and in the USA the Food and Drug Administration (FDA).

There are various ways of developing pharmaceuticals. Many important new pharmaceuticals have been devel-

54 Levenbook, I. (2011): The role of non-human primates in the neurological safety of live viral vaccines. Biologicals 39 (1): 1-8.

55 Sodora, D.L., J.S. Allan, C. Apetrei, J.M. Brenchley, D.C. Douek, J.G. Else, J.D. Estes, B.H. Hahn, V.M. Hirsch, A. Kaur, F. Kirchhoff, M. Muller-Trutwin, I. Pandrea, J.E. Schmitz & G. Silvestri (2009): Toward an AIDS vaccine: lessons from natural simian immunodeficiency virus infections of African nonhuman primate hosts. Nat. Med. 15: 861-865.

Osorio, J.E., J.N. Brewoo, S.J. Silengo, J. Arguello, I.R. Moldovan, M. Tary-Lehmann, T.D. Powell, J.A. Livengood, R.M. Kinney, C.Y. Huang & D.T. Stinchcomb (2011): Efficacy of a tetravalent chimeric dengue vaccine (DENVax) in Cynomolgus macaques. Am. J. Trop. Med. Hyg. 84: 978-987.

Sullivan, N.J., L. Hensley, C. Asiedu, T.W. Geisbert, D. Stanley, J. Johnson, A. Honko, G. Olinger, M. Bailey, J.B. Geisbert, K.A. Reimann, S. Bao, S. Rao, M. Roederer, P.B. Jahrling, R.A. Koup & G.J. Nabel (2011): CD8+ cellular immunity mediates rAd5 vaccine protection against Ebola virus infection of nonhuman primates. Nat. Med. 17: 1128-1131.

oped directly through animal experimentation or using animal organs. Renowned examples of this include the development of insulin for treating Diabetes mellitus (diabetes), the development of beta-blockers for the treatment of heart and circulation problems (see boxes), as well as the development of acid inhibitors for treating ulcers. Within current pharmaceutical research, animal experimentation is being increasingly supplemented and replaced by non-animal experimentation – for example stroke research where the emergence of thrombi (blood clots) may be investigated in flow chamber tests.[56] However, the complete discontinuation of animal experimentation is not currently possible, nor will it be in the near future. As mentioned above, it would therefore also be incompatible with the Declaration of Helsinki.

Example

In 1921, Frederick Banting and Charles Best manufactured insulin for the first time as an extract from the pancreas, including inter alia dogs. Following James Collip's improvement to insulin isolation, it became possible to manufacture it in pure form out of the pancreas, which in the following year enabled *Diabetes mellitus*, i.e. diabetes, to be treated in patients.[57]

The development of new pharmaceuticals against *Diabetes mellitus* was also essentially based on animal experimentation, supplemented by non-animal experiments and classical studies on humans. One such new pharmaceutical group includes the analogues of the "Glucagon-like peptide" (GLP1). This hormone, which is released by the intestines following ingestion, improves the discharge of insulin from the pancreas, controls the release of other hormones, reduces bowel movement and appetite, and has an effect on further organs such as the lungs. All of these effects work together to reduce the blood glucose level[58]; this complex interaction may only be observed in experiments on animals. These experiments provided the foundation for the introduction of GLP1 analogues in diabetes therapies in 2005. Scientists also discovered from animal experimentation, mainly on pigs and dogs, that GLP1 is very quickly broken down, but that the DPP4 enzyme (dipeptidyltransferase 4) that is responsible for this may be blocked, thereby enabling the positive effects of GLP1 to be enhanced.[59] Corresponding pharmaceuticals (Gliptine) were approved in 2006 for the treatment of diabetes. Both classes of pharmaceuticals have brought significant progress in the treatment of diabetes, although they have not yet led to the normalisation of blood sugar levels, with the result that further research is necessary.[60]

56 Ruggeri, Z.M. (2009): Platelet adhesion under flow. Microcirculation 16: 58-83.

57 Banting, F.G., C.H. Best, J.B. Collip, W.R. Campbell & A.A. Fletcher (1922): Pancreatic extracts in the treatment of diabetes mellitus. Can. Med. Assoc. J. 12: 141-146.

58 Holst, J.J. (2007): The physiology of glucagon-like peptide 1. Physiol. Rev. 87: 1409-1439.

59 Deacon, C.F., L. Pridal, L. Klarskov, M. Olesen & J.J. Holst (1996): Glucagon-like peptide 1 undergoes differential tissue-specific metabolism in the anesthetized pig. Am. J. Physiol. Endocrinol. Metab. 271: E458-E464.

Deacon, C.F., S. Wamberg, P. Bie, T.E. Hughes & J.J. Holst (2002): Preservation of active incretin hormones by inhibition of dipeptidyl peptidase IV suppresses meal-induced incretin secretion in dogs. J. Endocrinol. 172: 355-362.

60 Tahrani, A.A., C.J. Bailey, S. Del Prato, A.H. Barnett (2011): Management of type 2 diabetes: new and future developments in treatment. Lancet 378: 182-197.

Example

The development of beta-blockers in the 1960s by James Black is a prototypical example of bioassays.[61] Bioassays are experiments carried out on isolated organs of specifically killed laboratory animals, for example isolated hearts or blood vessels. Black also carried out experiments on intact animals. These experiments enabled him to find substances that hinder the effects of the "stress hormone" adrenaline on blood vessels by blocking the effects of adrenaline on its receptors, the "beta-receptors". These substances, known as "beta-blockers", were able to reduce blood pressure and heart rates in laboratory animals. Today beta-blockers are one of the most frequently used pharmaceuticals and are used very successfully, amongst other things, to reduce high blood pressure, as a preventive treatment and aftercare for heart attacks, and, for several years now due to more recent clinical research involving experiments on animals, also for chronic cardiac failure and many further diseases. For example, death rates in cases involving chronic cardiac failure have fallen by more than one-third.[62]

4.3.3 Toxicological Investigation

Animal experiments are the classical procedures used to determine the toxicity of medicines, and chemicals in general. All medicines must be subject to a safety examination that complies with the experiments required by law prior to licensing, which also include animal experimentation. This includes testing for acute and chronic toxicity, carcinogenic effects and – since the Thalidomide Affair – teratogenic effects, i.e. any damage caused to the unborn.

Investigating the potential toxic effects of a pharmaceutical includes a range of methods, for example in vitro methods (in the test tube) not involving animal testing, after which substances that pass the initial tests are then used in animal experiments. This procedure is regulated in the recommendations of pharmaceutical authorities, which are often compiled at the international level (see box).

Significant progress has been achieved in the investigation of toxicity using methods not based on animal testing; this applies both for acute toxicity and for possible effects on offspring (known as reproductive toxicity[63]). This is due not least to the national and international development of corresponding methods and the establishment of national agencies for validating these methods; in Germany this function is performed by the Centre for the Documentation and Evaluation of Alternative Methods to Animal Experiments [Zentralstelle zur Erfassung und Bewertung von Ersatz- und Ergänzungsmethoden zum Tierversuch, ZEBET] at the Federal Institute for Risk Assessment [Bundesinstitut für Risikobewertung]. Analysis of acute toxicity with the LD50-Test is particularly harmful for laboratory animals, as this test determines the dose of a given pharmaceutical that results in half of the animals dying. Efforts have been pursued for years to abolish this test and to replace it with a newer, more sophisticated and meaningful procedure. In addition, the development of new animal models, such as replacing experiments on monkeys with experiments on pigs, has made significant progress.[64]

In 2006, the EU adopted a Chemicals Directive (Regulation no. 1907/2006 REACH – **R**egistration, **E**valuation, **A**uthorisation and **R**estriction of **C**hemicals), according to which chemicals that have been in use for a long time, but not yet tested, must be examined above a particular tonnage limit. The examination of

61 Black, J. (1996): A personal view of pharmacology. Annu. Rev. Pharmacol. Toxicol. 36: 1-33.

62 Bristow, M.R. (2011): Treatment of chronic heart failure with β-adrenergic receptor antagonists: a convergence of receptor pharmacology and clinical Cardiology. Circ. Res. 109: 1176-1194.

63 Schenk, B., M. Weimer, S. Bremer, B. van der Burg, R. Cortvrindt, A. Freyberger, G. Lazzari, C. Pellizzer, A. Piersma, W.R. Schäfer, A. Seiler, H. Witters & M. Schwarz (2010): The ReProTect Feasibility Study, a novel comprehensive in vitro approach to detect reproductive toxicants. Reprod. Toxicol. 30: 200-218.

64 Aigner, B., S. Renner, B. Kessler, N. Klymiuk, M. Kurome, A. Wünsch & E. Wolf (2010): Transgenic pigs as models for translational biomedical research. J. Mol. Med. 88: 653-664.

Bode, G., P. Clausing, F. Gervais, J. Loegsted, J. Luft, V. Nogues & J. Sims; Steering Group of the RETHINK Project (2010): The utility of the minipig as an animal model in regulatory toxicology. J. Pharmacol. Toxicol. Methods 62: 196-220.

all widely-used chemicals in the EU (estimated to be around 30,000) under the REACH Regulation includes both methods that do not involve animal experimentation and those which do. To avoid excessively high levels of animal experimentation, particular importance is given to the 3Rs Principle (see p. 1) and the development of methods that do not involve animal experimentation (see above). Nevertheless, this Regulation has led to a significant increase in animal experimentation figures.

Example

An example of a step-by-step procedure starting with cell cultures and moving through animal experiments to clinical trials is the procedure used to investigate potential causes of cardiac arrhythmias. The possible cause of cardiac arrhythmias is one of the most significant toxic effects of pharmaceuticals and frequently results in the end of pharmaceutical development – at every level of development. Such procedures are regulated through internationally adopted recommendations that are applied by the pharmaceutical authorities both in Europe and the USA.[65] To search for such effects, as a first step the (supposedly) responsible current flows are measured at – often genetically modified – cell lines or heart muscle cells (*in vitro* I_{Kr}-Assay). Substances that cause suspicious changes to these current flows are as a rule not developed further. Substances that do not appear to arouse suspicion at this level are investigated further on isolated hearts (cardiac current flows) and finally on drugged animals (cardiac current flows, ECG). Animal experiments are necessary, since the toxic effects may also be triggered indirectly, e.g. through metabolites of the substance. Suitable species involve dogs, non-human primates, pigs, rabbits, ferrets and guinea pigs – due to the similarity between their cardiac current flows and those of humans. From the overall perspective of the results, a decision is then taken as to whether the substances are sufficiently safe for use in humans. Above all, special precautionary measures must be followed during initial use in humans (e.g. ECG controls).

4.3.4 New Operating and Invasive Medical Procedures

The overwhelming majority of current clinical surgical procedures and their associated technologies has been tested on animals, predominantly on large animals such as pigs or sheep. During such experiments the operating techniques and procedures are tested and compared with one another, and materials and instruments

65 European Medicines Agency, Federal Drug Authority & International Conference on Harmonization (2005a): Guidance for Industry: S7B Nonclinical Evaluation of the Potential for Delayed Ventricular Repolarization (QT Interval Prolongation) by Human Pharmaceuticals. Available at: www.ema.europa.eu/ema/pages/includes/ document/open_document.jsp?webContentId=WC500002841. Downloaded on 21.01.12.

European Medicines Agency, Federal Drug Authority & International Conference on Harmonization (2005b): Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs. Available at: www.ema.europa.eu/ema/pages/includes/document/ open_document.jsp?webContentId=WC500002879. Downloaded on 21.01.12.

are developed and tested, thereby laying the foundation for their application on humans. This applies above all to the development of innovative procedures, more recently especially for implants or in transplant medicine.

The development of heart surgery is a prominent example of this, since it covers the development of surgical techniques themselves, i.e. bypasses, the replacement of heart valves, and through to heart transplants. A second prerequisite for open-heart surgery are methods for stopping the heart with the assistance of specially-cooled liquids, which were developed in a series of experiments on dogs. A recent example of such research, which was initially carried out on laboratory animals and subsequently developed, is that of growing heart valves for children.

A further area that has been intensively researched for many years is transplant medicine, where it is necessary to not only thoroughly investigate surgical procedures, but also preparation and aftercare, particularly problems relating to transplant rejection. A third area involves the large number of invasive internistic procedures, an example being the development and ongoing improvement of pacemakers and defibrillators (see boxes).

Example

Size-adaptable, i.e. growing, heart valves for implantation during childhood could not have been used clinically without experiments on large animals. Originally conceptualised as a model for examining enhanced biocompatibility (i.e. tolerance by the surrounding tissue) compared to other heart valves made from non-organic material, a growing sheep was used to provide (surprising) proof of the growth of heart valves manufactured through "tissue engineering". Thus far, such implants have been used in more than 50 patients, overwhelmingly children.[66] To date there have been no occurrences of degeneration, and no replacement operations have been necessary.

Example

An area in which there appears to be no alternative in a clinical-scientific and ethical perspective to investigation through animal experiments is organ transplantation. For example, innovative, cell therapy-based approaches to tolerance-induction in relation to the transfer of human hearts, lungs, livers or kidneys initially need to be tested through animal experimentation before their clinical use on humans can be justified. Complex processes involving organ transfers and cell-therapeutic changes to the immune response must be tested on an entire organism. Organ transfers to patients are only possible if these new strategies are successfully tested on animals. The benefit compared to the current procedure within transplant medicine is that it could be possible to avoid immunosuppression, along with its numerous side effects, which is currently still necessary.

66 Cebotari, S., I. Tudorache, A. Ciubotaru, D. Boethig, S. Sarikouch, A. Goerler, A. Lichtenberg, E. Cheptanaru, S. Barnaciuc, A. Cazacu, O. Maliga, O. Repin, L. Maniuc, T. Breymann & A. Haverich (2011): Use of fresh decellularized allografts for pulmonary valve replacement may reduce the reoperation rate in children and young adults: early report. Circulation 124 (11 Suppl.): 115-123.

Example

Non-operative invasive procedures are as a rule developed and tested in animal experiments prior to their application in humans. An example of this is the development of defibrillators, i.e. electronic equipment through which a heart attack can be stopped by ventricular fibrillation (= uncoordinated and very quick stimuli of the heart muscle). Both the discovery of ventricular fibrillation in the middle of the 19th Century and almost all attempts to end it with electrical pulses (since the end of the 19th Century) have been carried out in animal experiments using dogs. The use of such electrical impulses in humans started in the middle of the 20th Century, initially in the operating room on the opened upper body, and later also through the intact upper body.[67] Effective forms of electrical impulses were also developed in experiments on dogs.[68] This equipment has subsequently become so highly developed that it may be operated by non-experts, and is thus made available in public locations (such as airports and railway stations).

4.3.5 Animal Experimentation in Basic and Advanced Training

Animal experimentation is necessary during several stages of basic and advanced medical training, for example, in order to learn surgical techniques. This applies above all for procedures for which a high degree of fine motor skills must be learned, which cannot be achieved in humans without endangering the patient. Generally speaking, many operating techniques must be learned intensively before operating on humans. Alongside participation in operations, the acquisition of technical operational skills is particularly significant; accordingly, as part of their training, surgeons practise procedures on laboratory animals, which they then later apply to humans. An example for this is anastomosis, i.e. the sewing together of small blood vessels, which is essential in several areas of surgery – such as in ear, nose and throat surgery – in order to ensure the supply of blood to an organ. The stitching must be tight, but without constricting the blood vessel and restricting blood flow. The necessary technique may at present only be learned through practice on the corresponding small blood vessels of laboratory animals. Thus, laboratory animals are used in order to secure the quality of operations on humans.

This form of animal experimentation differs from the above examples through the fact that the goal pursued is not research, but rather training. The assessment and approval of such procedures must therefore follow other criteria than research products, which are each based on their own original goals.

4.4 Research on Non-Human Primates

Due to their evolutionary similarities, non-human primates are more closely related to humans than other animals. Various structures and functional principles have developed through evolution that are found exclusively in primates, which include humans, apes and monkeys. These structures and functions may therefore only be investigated on members of this mammal group. Non-human primates are used in many areas of biomedicine (immunology and infectiology, reproductive biology, neuroscience and pharmaceutical testing) as an important model system. This Statement will therefore refer to some of the most important examples.

Due to their evolutionary similarities to one another, humans and non-human primates often react to pathogens in a similar manner. Moreover, a range of important pathogens have developed that particularly affect primates.[69] The devel-

67 Zoll, P.M., A.J. Linenthal, W. Gibson, M.H. Paul & L.R. Norman (1956): Termination of ventricular fibrillation in man by externally applied electric countershock. N. Engl. J. Med. 254: 727-732.

68 Lown, B., R. Amarasingham & J. Neuman (1962): New method for terminating cardiac arrhythmias: use of synchronized capacitor discharge. J. Am. Med. Ass. 182: 548-555.

Flaker, G.C., J.C. Schuder, W.C. McDaniel, H. Stoeckle & M. Dbeis (1989): Superiority of biphasic shocks in the defibrillation of dogs by epicardial patches and catheter electrodes. Am. Heart. J. 118: 288-291.

69 Wolfe, N.D., C.P. Dunavan, J. Diamond (2007): Origins of major human infectious diseases. Nature 447: 279-283.

opment and examination of many important vaccinations, including above all the polio vaccine[70], was essentially based on experiments on non-human primates, as is current research on vaccines against life-threatening pathogens.[71]

Non-human primates also have high value in research into the functioning of the brain and its diseases. Research into the neurobiological foundations for sight, for which David Hubel and Torsten Wiesel were awarded the Nobel Prize for Medicine and Physiology in 1981[72], paved the way for an understanding of visual disorders in children (amblyopia, lazy eye) that involve strabism and the development of short-sightedness.[73] These studies, which were initially grounded in basic research, made it possible to achieve the best possible sight for affected individuals by implementing a timely prophylaxis or therapy for amblyopia.

The main progress in the development of neuroprostheses for the rehabilitation of patients suffering from paralysis following spinal cord injuries or strokes has been based on experiments on rhesus monkeys, where neuroprostheses and brain-computer interfaces measure brain activity in order to guide prostheses or computers.[74] These approaches are showing great potential to give back injured patients part of their freedom of action.[75] Studies on monkeys make a decisive contribution to the continuous improvement of neuroprostheses to ensure that restoring arm and hand movements for injured patients will be realistic.[76]

Within the field of neuroregeneration, studies are being conducted into nerve cell regrowth. The "Nogo" protein prevents the healing of damaged nerves in human adults following a spinal cord injury.[77] Experiments on monkeys have been able to demonstrate that antibodies developed to counter "Nogo" following spinal cord injuries lead to significant functional improvements through nerve growth.[78] Currently, "Nogo" antibodies are being used in clinical studies on patients with spinal cord injuries.

Most neuropsychiatric diseases, e.g. schizophrenia or attention deficit hyperactivity disorder (ADHS) are accompanied by brain dysfunction in the frontal lobe.[79] Research on rhesus monkeys is of decisive importance for decoding the mode of operation of the frontal lobe, which is specific to primates.[80] A significant impetus for developing drug-

70 Sabin, A.B. (1965): Oral poliovirus vaccine. History of its development and prospects for eradication of poliomyelitis. J. Am. Med. Assoc. 194: 872-876.

71 Lin, H., D.E. Griffin, P.A. Rota, M. Papania, S.P. Cape, D. Bennett, B. Quinn, R.E. Sievers, C. Shermer, K. Powell, R.J. Adams, S. Godin & S. Winston (2011): Successful respiratory immunization with dry powder live-attenuated measles virus vaccine in rhesus macaques. Proc. Natl. Acad. Sci. USA 108: 2987-2992.

Daubersies, P., A.W. Thomas, P. Millet, K. Brahimi, J.A.M. Langermans, B. Ollomo, L. BenMohamed, B. Slierendregt, W. Eling, A. Van Belkum, G. Dubreuil, J.F.G.M. Meis, C. Guérin-Marchand, S. Cayphas, J. Cohen, H. Gras-Masse & P. Druilhe (2000) Protection against Plasmodium falciparum malaria in chimpanzees by immunization with the conserved preerythrocytic liver-stage antigen 3. Nature Med. 6: 1258-1263.

72 Hubel, D.H., T.N. Wiesel, S. LeVay (1976): Functional architecture of area 17 in normal and monocularly deprived macaque monkeys. Cold Spring Harb. Sym. 40: 581-589.

73 Barrett, B.T., A. Bradley, P. McGraw (2004): Understanding the neural basis of amblyopia. Neuroscientist 10: 106-117.

74 Green, A.M., J.F. Kalaska (2011): Learning to move machines with the mind. Trends Neurosci. 34: 61-75.

75 Hochberg, L.R., M.D. Serruya, G.M. Friehs, J.A. Mukand, M. Saleh, A.H. Caplan, A. Branner, D. Chen, R.D. Penn & J.P. Donoghue (2006): Neuronal ensemble control of prosthetic devices by a human with tetraplegia. Nature 442: 164-171.

76 Velliste, M., S. Perel, M.C. Spalding, A.S. Whitford & A.B. Schwartz (2008): Cortical control of a prosthetic arm for self-feeding. Nature 453: 1098-1101.

77 Schwab, M.E. (2004): Nogo and axon regeneration. Curr. Opin. Neurobiol. 14: 118-124.

78 Freund, P., E. Schmidlin, T. Wannier, J. Bloch, A. Mir, M.E. Schwab & E.M. Rouiller (2006): Nogo-A-specific antibody treatment enhances sprouting and functional recovery after cervical lesion in adult primates. Nature Med. 12: 790-792.

79 Robbins, T.W. & A.F. Arnsten (2009): The neuropsychopharmacology of fronto-executive function: monoaminergic modulation. Annu. Rev. Neurosci. 32: 267-287.

Nelson, E.E. & J.T. Winslow (2009): Non-human primates: Model animals for developmental psychopathology. Neuropsychopharmacol. 34: 90-105.

80 Castner, S.A., G.V. Williams & P.S. Goldman-Rakic (2000): Reversal of antipsychotic-induced working memory deficits by short-term dopamine D1 receptor stimulation. Science 287: 2020-2022.

free treatment for psychiatric diseases is expected from this research branch.[81]

Investigations on non-human primates are important for research into ageing[82] and the investigation of neurodegenerative diseases. For example, MPTP (1-Methyl-4-Phenyl-1,2,3,6-Tetrahydropyridine)-primate models are used to decode the pathology of Parkinson's disease and to develop therapies.[83] Non-human primates that are exposed to MPTP develop symptoms similar to Parkinson's disease. This has made it possible to discover the pathological consequences of Parkinson's disease, and thus a range of therapeutic approaches have become possible, for example the targeted administration of dopamine agonists and the use of deep brain stimulation ("brain pacemakers").[84] Specifically, deep brain stimulation is a new and effective procedure for treating patients with movement disorders that would have been barely conceivable without research on primates.[85]

This range of examples should stress the importance of non-human primates for gaining an understanding of physiological processes as a prerequisite for targeted healing and treatment approaches for disease. Due to our evolutionary similarity, results from experiments on non-human primates are most readily transferable to humans compared to those of all other animal species. Knowledge gained from carefully conducted experiments on primates is beneficial for medical progress and hence for humans. Experiments on primates are only carried out if, due to the complexity of physical processes within living organisms, they cannot be replaced by alternative methods. Such experiments therefore remain an important pillar of responsible biomedical research.

4.5 Transferability of the Results of Animal Experiments to Humans

The question arises in relation to research involving animal experimentation for the benefit of humans as to whether the results obtained from animals can be transferred to humans. This applies to research into the causes of disease and new therapeutic strategies, as well as the investigation of toxic effects.

In principle, the physiological structures of humans and other vertebrates are similar – which may be recognised from the basic anatomical, biochemical and physiological similarities of structure and function that have resulted from their evolutionary and genetic affinities. This means that most pharmaceuticals have similar effects on humans and animals. This may be discerned not least in the fact that many pharmaceuticals are used on humans and animals for the same diseases and for the same purposes. Veterinary pharmaceuticals belong to the same categories, use the same mechanisms and frequently also contain the same substances as the corresponding human pharmaceuticals; such data is available in the Anatomic Therapeutic Chemical (ATC) classification system of drug coding used by the WHO.[86]

81 Goldman-Rakic, P.S., S.A. Castner, T.H. Svensson, L.J. Siever & G.V. Williams (2004): Targeting the dopamine D1 receptor in schizophrenia: insights for cognitive dysfunction. Psychopharmacology 174: 3-16.

82 Roth, G.S., J.A. Mattison, M.A. Ottinger, M.E. Chachich, M.A. Lane & D.K. Ingram (2004): Aging in rhesus monkeys: relevance to human health interventions. Science 305: 1423-1426.

83 Capitanio, J.P. & M. Emborg (2008): Contributions of non-human primates to neuroscience research. Lancet 371: 1126-1135.

84 Jenner, P. (2003): The contribution of the MPTP-treated primate model to the development of new treatment strategies for Parkinson's disease. Parkinsonism Relat. Disord. 9: 131-137.

85 Rosin, B., M. Slovik, R. Mitelman, M. Rivlin-Etzion, S.N. Haber, Z. Israel, E. Vaadia & H. Bergman (2011): Closed-loop deep brain stimulation is superior in ameliorating parkinsonism. Neuron 72: 370-384.

86 WHO Collaborating Centre for Drug Statistics Methodology (2012): The Anatomical Therapeutic Chemical (ATC) classification system and the ATCvet system for classification of veterinary medicines. Available at: www.whocc.no und www.whocc.no/atcvet/. Downloaded on 23 January 2012.

Due to the similarities between animal and human physiology and pharmacology, animal experiments are of central importance for investigating the efficacy and innocuousness of pharmaceuticals, diagnostics and therapeutic processes. However, it must be pointed out that these are similarities only, and that the situations are not identical. This means that there are individual, at times even significant, variations, for example between the reactions of human and animal organisms to pharmaceuticals – as there are also differences between individual human individuals (e.g. genotypes). Therefore, compared to in vitro data considered in isolation, while animal experimentation does provide additional certainty, it is not absolute. Animal experiments are thus carried out prior to clinical testing on various animal species to increase certainty levels.

Despite individual negative examples and resulting doubts regarding the reliability of animal experimentation as a predictive tool[87], the problem of result transferability is not as great as is occasionally portrayed.[88] Comprehensive analysis of the effects of pharmaceuticals[89] have arrived at the conclusion that the overwhelming portion of intended effects, and up to 60 to 70 percent of the unintended effects of pharmaceuticals on humans may be correctly predicted through animal experimentation. These percentages appear to be too low considering the fact that the development of practically-all pharmaceuticals in which toxic effects are discovered during pre-clinical studies is stopped, with the result that their predicted toxic effects are never investigated in humans. This means that the transferability of results is high, but does not reach 100 percent. However, it is also important that precise results be obtained from animal experiments for predictive purposes. This in turn requires – due to the known fluctuations in biological experiments and the fact that certain undesired effects are rare – a sufficient number and a sufficient degree of repetition of such experiments.

An argument that is used against transferability relates to the market recalls of pharmaceuticals due to dangerous undesired effects. Since licensing pharmaceuticals requires non-animal experimentation methods, animal experimentation and then clinical trials on patients (normally several thousand patients prior to approval) in this order, some potential problems will not have been sufficiently identified through all of these experiments. This is caused by the fact that the concerned damage is very rare: if a serious toxic effect only arises in 1 out of every 100,000 individuals treated, then it will be highly unlikely that it will be discovered in the 5,000 to 10,000 people treated in studies prior to approval. For this reason, in all cases new pharmaceuticals are subject to a requirement of prescription, in order to ensure that they are used under medical supervision.

These market recalls show that all of the steps followed before a pharmaceutical is licensed require ongoing improvement. Much can be learned to improve future development and approvals, particularly from the retrospective analysis of such problems. Examples involve both recalls of broadly used pharmaceuticals

87 Pound, O., S. Ebrahim, P. Sandercock & M.B. Brachen (2004): Where is the evidence that animal research benefits humans? BMJ 328: 514-517.

Matthews, R.A.J. (2008): Medical progress depends on animal experiments – doesn't it? J. Roy. Soc. Med. 101: 95-98.

88 Bakhle, Y.S. (2004): Missing evidence that animal research benefits humans: evidence is all around us. BMJ 328: 1017.

Blakemore, C. & T. Peatfield (2004): Missing evidence that animal research benefits humans: moratorium is unjustified. BMJ 328: 1017-1018.

89 Löscher, W. & H. Marquardt (1993): Sind Ergebnisse aus Tierversuchen auf den Menschen übertragbar? [Can the results of animal experiments be transferred to humans?] Deut. Med. Wochenschr. 118: 1254-1263.

Olson, H., G. Betton, D. Robinson, K. Thomas, A. Monro, G. Kolaja, P. Lilly, J. Sanders, G. Sipes, W. Bracken, M. Dorato, K. Van Deun, P. Smith, B. Berger & A. Heller (2000): Concordance of the toxicity of pharmaceuticals in humans and in animals. Regul. Toxicol. Pharm. 32: 56-67.

such as COX2 inhibitors (Coxibe)[90], as well as incidents that occur during the development of pharmaceuticals.[91] Such analysis has resulted in improved guidelines for the initial use of new pharmaceuticals in humans, including required safety precautions.[92]

Within this safety context, various animal species have proven to be particularly relevant in relation to various issues. Whilst most animal experiments are carried out on mice, followed by rats, other species are more appropriate for particular questions if they are closer to humans with regard to the areas in question. This particularly applies for pigs and dogs for research into heart and circulatory diseases.

In recent years the use of genetically modified animals has become increasingly important in animal experimentation. This applies in particular to mice, and to a lesser extent to other species such as pigs, whose physiology is more similar to that of humans.[93] By switching off or modifying individual genes it is possible to imitate genetically-dependent diseases, as well as other diseases. Even though these models are not perfect, they often represent the only possibility for investigating diseases without using patients. Work is also progressing into how to carry out experiments on mice that could otherwise only be conducted on primates – such as by rendering mice susceptible to viruses (HIV, Hepatitis C) that normally only affect humans and some species of non-human primates.[94]

90 Wallace, J.L. (1999): Selective COX-2 inhibitors: is the water becoming muddy? Trends. Pharmacol. Sci. 20: 4-6

Grosser, T., Y. Yu & G.A. Fitzgerald (2010): Emotion recollected in tranquility: lessons learned from the COX-2 saga. Annu. Rev. Med. 61: 17-33.

91 Duff, G.W. (2006): Expert Scientific Group on Phase One Clinical Trials – Final Report. TSO The Stationery Office. Norwich, UK. Available at: http://www.trialformsupport.com/business/doc/ Final_Report_of_the_Expert_Scientific_Group_%28ESG%29.pdf. Downloaded on 23 January 2012.

Hansel, T.T., H. Kropshofer, T. Singer, J.A. Mitchell & A.J. George (2010): The safety and side effects of monoclonal antibodies. Nat. Rev. Drug. Discov. 9: 325-338.

92 European Medicines Agency (2007): Guideline on strategies to identify and mitigate risks for first-in human clinical trials with investigational medicinal products. Available at: www.ema.europa.eu/ema/pages/includes/ document/open_document.jsp?webContentId=WC500002988. Downloaded on 23 January 2012.

93 Aigner, B., S. Renner, B. Kessler, N. Klymiuk, M. Kurome, A. Wünsch & E. Wolf (2010): Transgenic pigs as models for translational biomedical research. J. Mol. Med. 88: 653-664.

Bode, G., P. Clausing, F. Gervais, J. Loegsted, J. Luft, V. Nogues & J. Sims; Steering Group of the RETHINK Project (2010): The utility of the minipig as an animal model in regulatory toxicology. J. Pharmacol. Toxicol. 62: 196-220.

94 Stoddart, C.A., E. Maidji, S.A. Galkina, G. Kosikova, J.M. Rivera, M.E. Moreno, B. Sloan, P. Joshi & B.R. Long (2011): Superior human leukocyte reconstitution and susceptibility to vaginal HIV transmission in humanized NOD-scid IL-2Rγ(-/-) (NSG) BLT mice. Virology 417: 154-160.

5. Concrete Recommendations and Commentary on the Transposition of the EU Directive

On 23 May 2012, the Federal Government approved draft legislation amending the Law on Animal Protection. This legislation addressed issues that the Academies had identified in the original draft put forth by the Federal Ministry for Food, Agriculture and Consumer Protection and that were recommended for clarification. However, new aspects were also introduced into the discussion from the other side, for example by the Bundesrat. This has made it necessary to review the original Academy Statement from March 2012. The present version addresses these changes in the comments on the draft legislation.

5.1 General Comments

The draft legislation and regulations largely reflect the provisions of the EU Directive, along with the previous legal position. These provisions are to be welcomed where they provide for the updating and clarification of the goals of animal experimentation work, the resumption in the use of animals, the establishment of good standards and the expertise of staff, and where they reflect a scientific standpoint. However, on several points the freedom of research and the State's duty to protect the life and physical integrity of humans, which are protected under the Basic Law, need to be afforded greater weight compared to animal protection to strike a balance between basic rights and the State goal of animal protection as referred to in the reasons for the legislation. In so doing it must be remembered that this form of balancing is asymmetrical. Whilst animal protection is simply proclaimed as a general goal of the State (Article 20a of the Basic Law), freedom of research amounts to a classic individual defence right (Article 5(3) of the Basic Law). In addition, the State's duty to protect the life and health of the general public also calls for animal experimentation aimed at improving diagnosis and therapies in human medicine (Article 2(2) of the Basic Law).

5.1.1 Power to Issue Statutory Ordinances

The draft legislation grants the authority to issue more than 20 statutory ordinances. Such regulations, or secondary legislation issued by the government, may undoubtedly play a meaningful role in relieving the workload of the legislature. However, Article 80(1) of the Basic Law places stringent limits on the transfer of legislative powers, subject to the requirement that the content, purpose and scope of the authorisation be clearly stated in the parent statute, thereby preventing Parliament from "divesting itself of its responsibility as a legislative body" (Federal Constitutional Court, 78, 249 [272]). In addition, according to case law of the Federal Constitutional Court, it follows mandatorily from the Democracy Principle within the Basic Law that the parliamentary legislature must take all "materially significant decisions" itself and may not delegate them to the government. The important element here is "materially significant for the realisation of basic rights". It does not seem to unequivocally be the case that this "theory of substantive legislative reservation" has been considered sufficiently within all of the authorisations to issue secondary legislation along with Article 80(1) of the Basic Law. In several striking cases, the secondary legislator

has been empowered to impose overly far-reaching restrictions on freedom of research, whilst the corresponding conditions and prerequisites have not been specified with sufficient precision in the legislation. The following provisions provide examples of this:

- Section 7a(6) leaves the extension of the statutory provisions in new subject areas to the secondary legislator, whilst failing to specify the prerequisites for the associated new and additional encroachments upon basic rights.
- The same applies for Section 8(3), which grants blanket authority to the secondary legislator to determine the duration of procedures, time limits and the revocation of approval.
- Section 8(5) provides the possibility of retroactive assessment, and empowers the Ministry to regulate the procedure, the content of the assessment and the duties of cooperation of the applicant. Leaving aside the fact that it is not clearly stated what significance this assessment may have for the specific or further experimental projects of the same researcher, or of the same institution as the case may be, for the projects of other researchers or establishments, here too the power to determine new encroachments on basic rights is left to the government alone.
- Section 9(3) enables the Ministry to issue regulations covering further prerequisites for particular groups of animal experiments in excess of the statutory provisions, to prohibit them entirely, to limit them or to render them dependent upon compliance with additional requirements, without expressly stating which corresponding regulatory gaps exist within the law that would render such measures necessary.
- Moreover, it is striking that several authorisations to issue regulations (such as sections 7a(6), 8(4) and 8(6) of the draft legislation) contain the phrase: "insofar as necessary in order to implement the legal acts of the European Union". Here, insofar as reference is thereby made not only to Directive 2010/63/EU, but also the future legal acts of the EU, such a blanket and indiscriminate implementation instruction to the secondary legislator causes serious concern, as it may lead to the abolition of the theory of substantive legislative reservation, and thus the circumvention of the parliamentary legislator.

On both formal and substantive grounds, the requirement of consent by the Federal Ministry for Education and Research in relation to the empowerment of the Agriculture Ministry to issue regulations that is included in the amended draft legislation of 23 May 2012 is welcomed. The Agriculture Ministry has always been considered responsible for animal protection and thus has drafted the legislation. However, as suggested by the title of the underlying EU Regulation, the object of the regulation is solely the protection of animals used for experimental or other scientific purposes. The regulation thus has nothing whatsoever to do with an area relating to agriculture, but rather is centred on an area relating to science. The consequence drawn in the draft legislation that the Ministry for Research must be consulted during the adoption of the regulation is expressly welcomed.

Recommendation

It appears to be urgently necessary to subject the overall draft legislation to a review as to whether the requirements of Article 80(1) of the Basic Law and the theory of substantive legislative reservation of the Federal Constitutional Court have been complied with. At minimum, the shared responsibility of the Ministry for Research and the Agriculture Minis-

try over the issue of the regulation is unreservedly recommended.

5.1.2 Compliance Costs

The indeterminacy of the projected costs that will be incurred through compliance with the regulations on the keeping of animals is unsatisfactory. It may be presumed that high investment costs will be incurred over the coming years at many research locations in order to comply with future requirements. These requirements apply to universities, non-university research institutions, as well as industry in the same manner, and the authorities and institutions must also be prepared to implement the law. The long-term compliance costs (running costs) required to implement the measures provided for in the draft legislation may range from the tens to hundreds of millions of Euros, due to the thousands of approval procedures (each year) for procedures previously not subject to approval, and due to retrospective assessments. To secure the expertise of the scientific and technical staff and the authorities, and to improve animal protection in accordance with the EU Directive and the new draft legislation, it is also necessary that laboratory animal science is adequately studied and taught; corresponding departments must therefore be (re-)established in universities, the relevant study and education courses must be modified accordingly, and the necessary one-off and long-term funding must be allocated within budgets; these figures are expected to lie in the tens of millions. In a Statement of 6 July 2012, the Bundesrat stated its view that annual expenditures of EUR 45 million per year will be incurred solely for new staff and additional working time in universities and non-university research establishments.

The *one-off compliance costs* (*investments*) may be far higher and lie in the hundreds of millions or even the billions of Euros, and relate to the condition of buildings and infrastructure comprising the concerned facilities. This should apply to private sector establishments, but also particularly to those of the Federation and the States (research institutes and universities). Such improvements to infrastructure would be necessary in substantial respects, and their effect would meaningfully enhance the animal protection regulations contained in the law. These costs will have to be provided for out of the budgets of the concerned facilities. A comprehensive and precise estimation of the costs is essential, which must take account inter alia of investment costs, projected operating costs, staff costs, and the expansion of training capacity.

Recommendation

The data relating to compliance costs, particularly including the one-off and ongoing financial resources required, should be specified in as much detail as possible and incorporated into the draft legislation. Additional budgetary provision must be made for the costs borne by the public exchequer.

5.2 Comments on the Amended Draft Legislation of 23 May 2012

5.2.1 Approval – Sections 7a and 8

The draft retains the regulatory technique chosen under previous legislation, whereby first the material prerequisites for implementing animal experimentation are laid down (Section 7a), and then in the following paragraph, the formal examination programme of the approval authorities is regulated (Section 8). This results in a loss of transparency. Under the current regulatory structure, several aspects appear to be necessarily duplicated, whilst others are specified without concrete addressees. For instance, it is unclear why Section 7a(2) of the draft mostly chose formulations such as “shall be based on”, “may only be carried out”, etc., whilst the second sentence provides that: “An examination shall be conducted as to whether or

not the purpose pursued can be achieved using other methods or procedures". Irrespective of the fact that an examination is not a "principle", it is not sufficiently clear what the consequences of a mere "examination" may or should be. On the other hand, it is clear in Section 8 that – as is the case under applicable legislation – a decisive element in the granting of approval is the scientifically-grounded presentation of the decisive points by the applying researcher.

Removing the provision that animal experiments are only permitted "[...] where their purpose cannot be achieved in another manner, including in particular through video footage" is welcomed. The regulation used in the previous Law on Animal Protection is redundant for the purposes of Sections 7a and 8. In particular, Section 7a stipulates that animal experiments must be "indispensable" for the achievement of the purposes specified. Where other methods are available for achieving the specified purposes, the requirement of indispensability will no longer be met, and hence the experimentation will not be permissible. A more detailed specification of individual alternative methods is thus not necessary; its exclusion from the passage referred to is logical and results in textual streamlining.

Recommendation

It should be examined whether the tendency to generate a lack of transparency arising out of the co-existence of these core provisions in Sections 7a and 8 may be removed by textual streamlining and by clarifying the relevant addressees of the regulations, thereby achieving a more easily understandable formulation. This would have a beneficial effect on legal certainty and the equal application of the rules by the approval authorities.

5.2.2 Minimisation of Suffering – Sections 7 and 7a

The draft legislation frames the decisive criterion in Section 7(1) and Section 7a(2) of the "species-specific capacity of the animals used to suffer from the effects of the experimentation". From a natural science perspective, it is welcomed that the previously used, although unsuitable, criterion of the neurophysiological sensitivity level establishing a pre-eminent status for vertebrates above invertebrates has been concretised in this manner. This is because invertebrate animals may be more advanced than vertebrates in the development of particular sensory organs. Even within the group of vertebrate animals, no unequivocal criterion can be inferred from sensory physiology that supports the special position of mammals and birds above fish. Moreover, sensory physiology may not be regarded as decisive, specifically in relation to animal protection issues. This is because an animal that is less developed in terms of neurophysiological sensitivity may under certain experimental conditions suffer more than a more highly-developed animal. The sole scientifically sustainable criterion is thus a consideration of the animals' capacity for suffering. This applies to both animal protection issues as well as freedom of research.

Recommendation

Rather than using the level of neurophysiological sensitivity that was previously regarded as decisive, the criterion of capacity to suffer harm must be applied. The formulation currently used in the draft legislation should be approved in this form.

5.2.3 Training – Section 7(2)

The draft legislation (Section 7(2), sentence 2, no. 3, in conjunction with Section 7(2), sentence 1, nos. 1 to 3) incorporates intrusion or treatment for the purpose of basic and advanced training into the definition of animal experimentation, where such action may involve "harm" for the

animals. However, according to the EU Directive (Article 3), this is only the case if the use on animals is "likely to cause lasting harm equivalent to, or higher than, that caused by the introduction of a needle in accordance with good veterinary practice". The draft legislation thus contains a more stringent national measure, which is not compatible with Article 2 of the EU Directive.

In Article 42(1), the EU Directive provides for a "simplified administrative procedure for projects ... that are necessary to satisfy regulatory requirements, or which use animals for production or diagnostic purposes with established methods". The EU Directive requires qualified training for all individuals involved in animal experimentation.

Recommendation

An examination should be carried out as to whether basic and advanced training may be deemed to constitute regulatory measures for the purposes of the Law on Animal Protection, and hence be subjected to a simplified procedure (comparable to reporting).

5.2.4 The Purposes of Animal Experimentation – Sections 7 and 7a

The draft legislation only partly implements the provisions of the EU Directive in relation to the admissibility and purposes of animal experimentation. Removing individual purposes such as the prevention or treatment of plant diseases or anomalies runs contrary to the basic motivation of the EU Directive, which calls for a pan-European harmonisation of framework conditions, under which animal experimentation is permitted. Therefore, all of the purposes of animal experimentation listed in the EU Directive must also be incorporated into the German Law on Animal Protection.

Recommendation

All of the goals of research and training specified in Article 5 of the EU Directive should be incorporated into the draft legislation.

5.2.5 The Termination of Animal Experimentation – Sections 7 and 7a

Breeding transgenic animals falls within the scope of the Law on Animal Protection if pain, suffering or harm is likely for the animals. Under current regulations, lines bred from the F2 generation onwards do not fall within its scope. It is not clear under the new statutory wording when the change occurs from the generation of new lines, which is deemed to constitute animal experimentation, to the pure further breeding of these lines pursuant to Section 11b(4) of the Law on Animal Protection. The previous regulation, which set this changeover after the F2 generation, has been tried and tested and should be retained.

Recommendation

The Law on Animal Protection should clarify that the change from animal experimentation to the further breeding of transgenic animal lines occurs after the F2 generation. Further breeding does not amount to animal experimentation.

5.2.6 Suitability of Experimental Leaders – Section 8

Section 8(1), no. 2 of the draft legislation regulates the individual prerequisites applicable to the leader of experimental procedures and his substitutes, which extend beyond technical suitability. The wording used here: "[...] and there are no circumstances which give cause for concern regarding their reliability", is legally problematic due to its indeterminacy. It is always possible to raise concerns against an individual that are not specified in any further detail. The regulation may consequently result in arbitrary decisions.

Recommendation

The wording "[...] and there are no circumstances which give cause for concern regarding their reliability" should be replaced. As in other administrative law situations, it should rather stipulate "[...] and there are no circumstances which establish their unreliability".

5.2.7 Non-technical Summaries and Intellectual Property – Section 8

Section 8(6) empowers the Federal Ministries to adopt a regulation governing the publication of summaries of approved experimental procedures. However, this regulation only partially affects the provisions of the EU Directive. Article 43 of the EU Directive provides that non-technical summaries shall be prepared "subject to safeguarding intellectual property and confidential information" and that they "shall not contain the names and addresses of the user and its personnel". Considering the high level of specialisation within research, inferences may be easily drawn to individuals and locations and concrete experimental projects despite their being anonymous. This particularly applies if project goals, including the number and type of animals used must be specified, as provided for under Section 41 of the draft regulation from January 2012 in relation to the publication of summaries. The present regulation does not sufficiently account for the legal interests of researchers and falls unnecessarily short of the EU Directive. Moreover, regulations relating to data protection with regard to the substantive legislative reservation should not be delegated to the secondary legislator, but rather clearly regulated in the primary legislation (law).

Recommendation

Article 43 of the EU Directive should be precisely implemented and include an express reservation of the protection of intellectual property and confidential information. Regulations on data protection should be clearly established in primary legislation.

5.2.8 Simplified Procedure – Section 8a

The possibility of a simplified procedure provided for under Section 8a of the draft legislation is welcomed. Any revision of this procedure in a future regulation should ensure that the procedure is actually simpler than the ordinary approval procedure, and that it draws on the previous reporting procedure with processing times that are as short as possible. This is of particular significance for the competitiveness of German biomedical research.

Recommendation

Care should be taken while issuing the regulation under Section 8a(5) to ensure that the simplified procedure is actually framed in simpler terms than the ordinary approval procedure. A simplified procedure should be based on the previous reporting procedure.

5.2.9 Staff Qualifications – Section 9

It is incomprehensible why the old wording of section 9(11) of the Law on Animal Protection should not be retained, since it is clear and substantively correct. Moreover, the technical classifications (veterinarian, physician, biologist, etc.) were removed and the list reformulated in the draft regulation from January 2012, along with different standards for recognising qualifications. The EU directive makes no provision for a different assessment of the professional qualifications of various occupational groups, and qualified biologists are unjustifiably subjected to less favourable treatment (see also the comments on section 10).

Recommendation

If technical qualifications and expertise are documented, there should be no different assessment of academic occupational groups compared to the position under the Law on Animal Protection.

5.2.10 Animal Protection Officials – Section 10

Section 10 regulates the powers of animal protection officials. The draft legislation fortunately did not specify the groups of individuals eligible to hold this position. However, the draft regulation from January 2012 stipulated that it should be occupied on principle by a veterinarian, whilst other occupational groups should only hold this position with exceptional approval. This is not appropriate and cannot be implemented, considering that approximately 300 new animal protection officials would shortly require appointment. The limitation to veterinarians reflects neither the actual situation nor the international state of the art in research involving animal experimentation.

Recommendation

The provisions of the previous Law on Animal Protection pertaining to individuals who are eligible to be appointed animal protection officials should be retained. Accordingly, all relevant academic occupational groups (natural scientists, veterinarians, and physicians) holding a relevant qualification should be eligible to be appointed animal protection officials.

5.2.11 Competence of the Advisory Board – Section 15

Section 15 of the draft legislation grants the competent authorities a right under national law to convene one or more advisory boards. The previous provisions were expanded, with the effect being that under the draft legislation, boards may also be convened for the "… assessment of reported changes to approved experimental procedures…". The authorities decide independently on requests for changes. The EU Directive makes no provision for the involvement of boards in approval procedures; therefore it is not clear why these more stringent provisions have been stipulated, which go beyond those of the Directive and the applicable Law on Animal Protection. Rapid decisions are necessary in relation to animal protection and research, for instance to quickly implement animal-friendly methods. However, the draft regulation from January 2012 does not state a clear position in this regard.

Recommendation

The competent authorities should be able to rule directly on applications for changes, as was done previously.

5.2.12 Advisory Boards – Section 15(4)

In its current version the Law on Animal Protection regulates, on the legislative level, the composition and expertise of the boards provided for under Section 15. In future this is to be determined by regulation. Since the requirements for establishing these advisory boards are not laid down in the Directive, but rather through existing national animal protection law, it is not clear why a basis in the Law on Animal Protection cannot be retained.

Recommendation

Regulations on the composition and expertise of the boards provided for under Section 15 should continue to be regulated under the Law on Animal Protection and not under other regulations.

5.2.13 National Committee – Section 15a

The EU Directive makes provision in Article 49 for the establishment of a national committee that "shall advise the competent authorities and animal welfare bodies on matters dealing with the acquisition, breeding, accommodation, care and use of animals in procedures and ensure sharing of best practice". Fulfilling this task calls for scientific expertise on the part of its members and a basic knowledge of the current state of methodological development.

Recommendation

The national committee should be established at a research institute dedicated to animal experimentation, and its mem-

bers should represent a broad spectrum of animal experimentation methods, including ethical questions of research involving animal experimentation.

5.3 Comments on the Draft Regulation

5.3.1 Expertise Requirements – Sections 3, 4 and 16

Sections 3, 4 and 16 of the draft regulation on the implementation of the EU Directive require that the expertise of staff responsible for the care and killing of animals for animal experimentation be ascertained, and that the staff members regularly attend advanced training courses (Section 3(2)). However, the draft regulation does not specify either precise periods for advanced training or standards for the training of specialist staff. The expertise requirements should thus be re-defined in the regulation. The Academies therefore expressly support the concrete formulation of teaching materials for the basic and advanced training of scientists and specialist staff involved in the implementation of animal experimentation. The same expertise should also be required of decision-makers at the approval authorities.

To provide a general guarantee of expertise on the part of the staff involved in animal experimentation, a corresponding certification of expertise should be provided according to the same standards throughout the country for all individuals involved in animal experimentation.

Such certification should be obtained through special training, either as part of a professional training programme or during study, or alternatively through additional training. As mentioned in the discussion of compliance costs, existing training capacity is insufficient, particularly in the universities. The basic and advanced training capacities required for the new regulations would have to be expanded in both the technical and the scientific sectors. Additional research is necessary to reduce, improve or replace animal experimentation, as required under the 3Rs Principle. To guarantee this research takes place, and to orient training around scientific progress, it will be necessary to establish professorships in the area of animal protection and laboratory animal science.

Recommendation

The regulations on the certification of expertise should be clearly formulated and comply with the requirements under the EU Directive. The expertise requirements should also apply to decision-makers in the approval authorities.

5.3.2 Animal Protection Officials – Section 5

The proposed provisions in Section 5(2) of the draft regulation on the implementation of the EU Animal Protection Directive stipulate that (at least as a general rule) only individuals holding a university qualification in veterinary medicine should be eligible to be appointed an animal protection official. However, this rule does not give consideration to the current content of courses in veterinary medicine or the experimental sciences. As at other points in the regulation (such as Section 16(1)), this function should also be open to appropriately trained natural scientists and physicians, which complies with the more broadly-worded EU Directive (Article 25).

Recommendation

The position of Animal Protection Official should be opened up to the class of individuals specified under Article 25 of the EU Directive, or under the previous provisions of the Law on Animal Protection.

5.3.3 Identification – Section 9

Section 9 stipulates that the draft regulation on the requirement for dogs, cats and primates be identified. Individual mark-

ing may also be necessary for other animal species for breeding, holding and preparing for experimentation. This section forms a part of good practice when dealing with animals. Established methods of individual marking (e.g. ear marking and transponders) should therefore be possible to use without express approval.

Recommendation

It should be expressly specified that current methods of identifying animals, in addition to the three methods mentioned above, do not constitute animal experimentation subject to a requirement of approval or reporting.

5.3.4 Designation of Participants – Section 13

The requirement that all individuals involved be designated pursuant to Section 13(1) entails that the authorisation should specify the individuals referred to in Section 12, sentence 1, nos. 3 to 5. Section 13(2) stipulates that a "change to the individuals specified in paragraph 1 or a change to the nature of the animals involved designated pursuant to Section 12, sentence 1, no. 1" must be promptly reported to the authorities. Both rules appear to be disproportionate, and will entail major bureaucratic efforts during implementation. It would be as if hospitals were required to report every change to medical or nursing staff to the relevant health authorities.

Recommendation

The regulations on the designation and duty to report potential changes to all individuals involved in the procedure should be reviewed. Only changes to responsible individuals should be subject to required reporting.

5.3.5 Post-Conclusion Procedure – Section 28

Contradictions also exist between the old Law on Animal Protection and the EU Directive in terms of regulating the applicable procedures following animal experimentation. The old Law on Animal Protection drew distinctions between different animal species with no basis in biology, and which have accordingly not been included in the EU Directive. The EU Directive provides for special status for non-human primates (particularly great apes), dogs and cats. This was transposed accordingly into Sections 8 and 9 of the draft regulation. The same should also apply for Section 28.

Recommendation

The provisions of the EU Directive should be transposed verbatim.

5.3.6 Classification of Severity – Section 31

The harm caused to animals during animal experiments is of major importance for their assessment, approval and implementation. It is therefore astonishing that neither the draft statute nor the draft regulation clarifies who is responsible for this classification. It would make sense if the National Committee provided for under Section 47 were to draft assignment criteria as part of implementing Annex VIII to the EU Directive, and if provision were made in Section 31 of the regulation for the applicant to classify the relevant harm categories in its application. Examining these categories should form part of the plausibility review carried out by the authorities based on the scientifically grounded representations of the applicant.

Recommendation

Section 31(2) no. 2 should be supplemented by the words in italics: "2. establish in a scientifically grounded manner that the prerequisites laid down in Section 8(1), sentence 2, no. 1, letters a and b of the Law on Animal Protection have been met and under which classification of harm the animal experimentation is to be designated". Section 31(2), no. 1, letter G may therefore be excised.

5.3.7 Approval of Multiple Similar Projects

In Article 40(4) the EU Directive stipulates "the authorisation of multiple generic projects carried out by the same user if such projects are to satisfy regulatory requirements or if such projects use animals for production or diagnostic purposes with established methods". Such multiple authorisation may contribute to a significant reduction in bureaucratic costs, as there would be no need to file and individually process multiple, similar applications for approval. Provision was made for group applications in relation to experimental procedures exempt from a requirement of approval under Section 37 of the draft regulation, although not in relation to procedures requiring approval.

Recommendation

The approval of multiple, similar projects carried out by the same user under Article 40(4) of the EU Directive should be included in the draft regulation.

5.3.8 Notification of Projects – Sections 36 and 38

The rules that apply to the notification of projects and the documents requiring submission have been formulated in very imprecise terms (Sections 36 and 38 of the draft regulation). The approval authorities are granted the possibility, without further specification, to examine cases subject to a requirement of notification, ultimately as cases requiring approval, and to demand the submission of all corresponding documents. This is because the authorities are not only required under Section 38 of the draft regulation to examine whether implementing the experimentation procedure under Section 16a(2) of the Law on Animal Experimentation should be prohibited, but also whether the prerequisites laid down in Section 8(1), sentence 2, nos. 1 to 8 of the Law on Animal Protection, all of which apply only to experimental procedures requiring approval, have been met. Moreover, pursuant to Section 36 of the draft regulation, the authorities may also require presentations under Section 31(1), sentence 2, nos. 2 to 4, which also relate to the prerequisites under Section 8. Significantly, the deadline for processing notifications pursuant to Section 36(2) is supposed to be 40 days, which is similar to the approval procedure under section 32. This results in a significant extension of the previously applicable notification procedure, for which the deadline was two weeks. This is not required under Article 42 of the EU Directive; provision is only made for the same time limits in relation to the approval procedure and the simplified administrative procedure in that the simplified administrative procedure may not last longer than the approval procedure.

Recommendation

Notification requirements for projects and the scope of official examinations of projects that are only subject to a requirement of notification – in contrast to the requirements applicable to approval and the corresponding scope of the official examination – need to be relaxed. In addition, the period after which the experimental procedures may be commenced needs to remain limited to the previous term of ten working days.

5.3.9 Publication of the Non-Technical Summary – Section 41

Section 41 of the draft regulation regarding the publication of the non-technical summary only briefly mentions that it should not contain any personal data. In its current version, Section 8(6) of the draft legislation does not take sufficient account of the justifiable interests of researcher confidentiality. This does not provide a sufficient guarantee of the right to intellectual property, data protection, and more generally the legitimate interests of researchers to expect that their projects and research goals are not disclosed in advance. For example, given such a high level of specialisation, it should hardly be

difficult given such a weak regulation to identify individual research procedures – despite being anonymous – and to draw inferences relating to individuals and locations. This particularly applies where project goals including the number and nature of the animals to be used must be included in this summary. Section 41 of the draft falls unnecessarily short of requirements under the Basic Law, but also of the confidentiality requirements laid down in Article 43 of the EU Directive, which is incompatible with Article 2 of the EU Directive. Article 43 of the EU Directive expressly stipulates that disclosure is to be made "subject to safeguarding intellectual property and confidential information".

Recommendation

Protecting intellectual property rights must be given greater consideration regarding the provisions of the Basic Law and the EU Directive.

5.3.10 National Committee – Section 47

It should be expected that significant functions will be vested in the National Committee (see also Section 47 of the draft regulation), which must strike a balance between the requirements of animal protection on the one hand, and scientific freedom on the other hand. Accordingly, the Federal Ministry for Education and Research should also have a significant right to be consulted in relation to its membership, and the committee should include independent experts from the area of animal experimentation – in a manner similar to current practice in Germany for ethics committees – in order to incorporate scientific expertise into the decision-making process. Provision should be made for appointments to be made in consultation between the Federal Ministry for Food, Agriculture and Consumer Protection and the Federal Ministry for Education and Research. Provision should also be made to ensure that the members of the committee possess the highest scientific expertise.

An important area of responsibility for the National Committee should be the completion of the conceptual definitions regulated in Annexes I to VIII of the EU Directive, as well as their revision according to ongoing scientific progress. These definitions would include the term "procedure", as well as the classification of the procedure as "minor", "medium" or "major".

Since science continuously progresses in all areas, including the development of research questions and techniques, the investigation of alternative methods, and the reduction of animal experimentation, a National Committee should be established at a scientific institution which, because of its tasks and activities, represents both animal protection aspects, as well as research interests, and possesses the requisite levels of knowledge and expertise.

Recommendation

The appointment of members to the National Committee should occur in consultation between the Federal Ministry for Food, Agriculture and Consumer Protection, and the Federal Ministry for Education and Research. Such a committee should be comprised of members with the highest scientific expertise.

6. Methodology

6.1 Occasion for, Commissioning of and Development of the Statement

On 22 September 2010, the European Parliament and the Council of the European Union adopted Directive 2010/63/EU on the protection of animals used for scientific purposes. Transposition into national law was to occur by 10 November 2012. On 9 January 2012 the Federal Ministry for Food, Agriculture and Consumer Protection presented draft versions of a "Third Law amending the Law on Animal Protection" and a "Regulation implementing Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes".

The German Academy of Sciences Leopoldina and the Union of German Academies of Sciences and Humanities took this as an opportunity to discuss the ethical and legal basis and importance and practice of research involving animal experimentation, and also to provide a critical commentary on the legislative process.

This Statement was drafted by a group of 14 scientists, and was subsequently presented to four experts. Their comments were considered and discussed in the definitive text adopted by the executive bodies of Leopoldina and the Union of German Academies of Sciences and Humanities. The Statement was finally approved on 22 February 2012 by the executive bodies of Leopoldina and the Union of German Academies of Sciences and Humanities.

On 23 May 2012, the Federal Government approved amended draft legislation amending the Law on Animal Protection. This addressed issues that the Academies had identified in the original draft by the Federal Ministry for Food, Agriculture and Consumer Protection and recommended for clarification. However, new aspects were also introduced into the discussion regarding the legislative procedure from the other side, including, for example, by the Bundesrat. This made it necessary to review the original Academy Statement from March 2012.

In September 2012, a revised version was adopted which contained specific comments and recommendations that took account of the Federal Government's amendments to the draft legislation.

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Notes

Other Publications

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The German National Academy of Sciences Leopoldina and the Union of the German Academies of Sciences and Humanities provide policymakers and society with independent, science-based guidance on issues of crucial importance for our future. The Academies' members are outstanding researchers from Germany and abroad. Working in interdisciplinary working groups, they draft statements that are published after being externally reviewed and subsequently adopted by the Standing Committee of the German National Academy of Sciences Leopoldina.

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