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Article

Why Do I Choose an Animal Model or an Alternative Method in Basic and Preclinical Research? A Spectrum of Reasons and Their Ethical Evaluation

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Simple Summary: Researchers in basic and pre-clinical research can use either animals or alternative methods. However, this choice is not always easy. It is influenced not only by personal beliefs and experience, but also by societal debates and opinions. In addition, the considerations that go into the decision are usually not made consciously. In this study, 13 people involved in relevant areas of medical research were interviewed, and the responses were qualitatively assessed and ethically analyzed. This paper presents 66 reasons why researchers use animals (41 %) or alternative methods (59 %). Many reasons are tied to the work environment (29 reasons) and to scientific standards (22). Such reasons are often pragmatic and can only be influenced to a limited extent. Other reasons were assigned to personal attitudes (11) and animal welfare (4). Even if few reasons can be rejected outright from an ethical point of view, there are good reasons to give some more weight than others, as a discussion of (exemplary) reasons shows. The study raises awareness of the decision-making process and the underlying reasons that we are often unaware of. This can help to reflect on and justify decisions. (190/200 words)

Abstract: Background: Little is known about the decisional background of choosing an appropriate disease model. Therefore, this paper aims, (1) to identify a *spectrum of reasons* for choosing between animal and non-animal disease models and (2) provides an *ethical analysis* of these reasons. **Methods**: 13 researchers from basic and preclinical research were interviewed, the interviews were analyzed qualitatively and the results were categorized. The ethical analysis was based on the principlism approach and a value judgement model. **Results**: This paper presents 66 reasons why researchers use animal (41 %) or alternative, non-animal disease models (59 %). Most of the reasons were be assigned to the work environment (29 reasons) and scientific standards (22 reasons). Other reasons were assigned to personal attitudes (11 reasons) and animal welfare (4 reasons). Qualitative relevant normative differences are presented in the ethical analysis. Even if few reasons can be rejected outright from an ethical point of view, there are good reasons to give some more weight than others. **Conclusions**: The spectrum of reasons and its ethical assessment provide a framework for reflection for researchers who may have to choose between animal models and (investing in) alternatives. This can help to reflect on and justify decisions. (199/200 words)

Keywords: basic and preclinical research; animal research; animal model; non-animal disease model; ethical reasoning; bioethics; qualitative research

1. Introduction

Ethical and regulatory background for using animals in basic and translational research

The question of *whether* and, if yes, *how* animal experiments should be carried out in biomedical research has not only been addressed in academic contexts, such as animal ethics, in the last three decades or so. It is also considered to be a controversial social and political issue due to housing conditions, the (sometimes perceived) reduced necessity due to increasing non-animal alternatives, and generally the fact that animals are subjected to stress, pain and harm, or even death [1,2]. Furthermore, in contrast to clinical research, where research is conducted as far as possible with

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humans for the benefit of *other humans*, animals are completely instrumentalized for the benefit of humans. In addition, there are well-known objections about the extent to which animal experiments are even "transferable" to humans and/or how much they can advance scientific knowledge in the biomedical field [3]. This is accompanied by the criticism that animal experiments which do not have sufficient scientific value fail to be ethically acceptable even if all other ethical requirements are fulfilled [4].

The gradual change in social and political attitudes towards animal experimentation over the last few decades [5] can also put pressure on biomedical researchers. Researchers conducting animal studies are increasingly subject to a regulatory and often related ethical obligation to provide justifiable reasons for the choice of an animal model as part of their *external* responsibility (towards society). Conversely, they are also subject to a scientific obligation as part of their *internal* responsibility (towards the scientific community) to provide reasons why not using an animal experiment and choosing alternative methods is justified. Alternatives roughly refer to all approaches that replace animals or (substantially) reduce their use in the research context. As long as the goals (research questions) are comparable, the strategies and approaches can be different. Therefore, researchers must make a choice between (basically) three courses of action (animal experiment, alternative, or no research), which, in normative terms, must be based on "good (= sufficiently justifiable) reasons" – be they ethical, epistemic (scientific) or, as the case may be, merely pragmatic. This choice, and the reasons for it, will be the focus of the following article.

It could be argued, however, that there is no *real* "choice" between the three options. Various political debates, especially in the European context, have eventually led to significant regulatory changes. One result is the European Union (EU) Directive 2010/63/EU [6]. However, this has been implemented differently at the national level [7,8]. According to this regulation and subsequent national interpretations, (e.g., in Germany), researchers are *legally obliged* to choose methods that do not require animals (replace), reduce the number of animals in the experiment (reduce) and improve the conditions of the animals used in the experiment (refine), whenever this is scientifically possible [6,9]. Although this restricts the freedom of research, it is difficult to argue ethically against this kind of restriction.

Decision-making and the role of ethics

Specific and binding restrictions can be seen especially in the field of *toxicology*. There are catalogues that define very precisely which disease model should be used for a particular test and whether there are validated non-animal alternatives (e.g., *OECD Guidelines for the Testing of Chemicals* Section 1, doi:10.1787/20745753) and validated alternative methods via the EU Science Hub "EU Reference Laboratory for alternatives to animal testing (EURL ECVAM)." Thus, the question of a choice rarely seems to arise: Either there is a validated alternative test, in which case it must be chosen, or the animal test is permitted (although the search for an alternative may be still desirable).

On the other hand, the research questions and objectives are structured differently in *basic and translational research*, and have a wider variation, for example, whether a chemical substance causes measurable skin irritation. The aim here is to test hypotheses and develop theories based on a disease model. These research methods and models must, therefore, fulfill other requirements than in the assessment of safety issues. Researchers in this field have more degrees of freedom than in toxicology.

Thus, it is often not clear in basic and translational research whether the use of a particular alternative method is really a *valid* alternative, i.e., if it leads to comparable results to the animal test, allows the testing of the same hypothesis or even maintaining the original research question. The use of an alternative can, therefore, often be a kind of experiment in itself, testing whether employing *in vitro* or *in silico* methods or new technologies, such as organoids or "organ on a chip," is comparable to the (originally used/planned) animal model.

Decision-making generally involves rational considerations, emotions and interests, both consciously and unconsciously. These considerations have to be balanced against each other. A number of value judgments play a role in this weighing process: *What value do I give to one argument or another? What is a "good" decision?* From an ethical and scientific perspective, it is desirable to make

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important decisions, such as the choice of a disease model, as consciously and systematically as possible [12]. In this context, ethics, as the systematic exploration of values, norms and principles, and as the critical examination of arguments involving (moral) value judgments, provides the relevant theoretical and methodological background. In this way, empirically stated reasons that play a role in decision-making can be classified thematically, on the one hand, and ethically evaluated, on the other, following methodological approaches of *empirical (bio)ethics* [13–15], which, in the meantime, have also found some counterparts in animal ethics [16,17].

Aims and Research Context

The aim of this paper is, therefore, (1) to identify a *spectrum of reasons* for choosing between animal models and alternative methods, empirically based on a qualitative interview study with researchers working in basic and translational biomedical research. Individual reasons and categories of reasons are then (2) discussed (exemplarily) from an ethical point of view, including the value judgments involved. The spectrum of reasons, the associated categorization and ethical assessment provide a framework for reflection for researchers who may have to choose between animal models and alternative methods.

That a certain reflective framework for such decisions might be useful became clear in the context of a larger research network, to which the research presented here also belonged. The R2N ('Replace' and 'Reduce') consortium from Niedersachsen (Lower Saxony)", https://r2n.eu/), funded by the Ministry of Science and Culture of the Federal State of Lower Saxony (Germany), consisted of 14 projects (12 life sciences projects, 2 ethics projects), and aimed at developing new alternative methods to reduce the number of animals used in experiments or replace specific animal experiments altogether, mainly in basic/preclinical and translational research. Selected results from one of the ethics projects (project R2N-E1) are presented here (related preliminary theoretical work has already been published in [19]); work from the second ethics project has also been published [20,21].

2. Materials and Methods

The results presented – the spectrum of reasons and the subsequent ethical discussion – are based on empirical and theoretical work [19].

Interview Study

An in-depth literature review and preliminary interviews with various experts concerned wih animal experimentation and/or alternative methods were conducted to become more familiar with the research field of basic and translational research involving animal experiments, and to develop the interview guide for the qualitative interview study. The conduct of the interview study was deemed unobjectionable by the ethics committee of Hannover Medical School.

Recruiting: In order to limit and define the scope of the decisions, the first step was to identify a suitable field of research. After a literature review, Alzheimer's research seemed to be suitable, as "classic" research in this field has been conducted extensively with animal models. However, there were also voices within the research community that had doubts about the suitability of the current animal model, which is why animal testing alternatives are also popular. We contacted a large number of researchers in the field of Alzheimer's research multiple times by mail and telephone. We only received one response. One possible reason for the failed recruiting could have been the COVID-19 pandemic. The interviews were planned and conduced in the period from April to June 2020 (during "lock down" in Germany). It is possible that this circumstance led to a lack of availability. However, we were unable to verify this hypothesis. We then decided to change our strategy and no longer limit ourselves to Alzheimer's research.

A snowball recruitment was initiated through expert recommendations via the R2N consortium; however, it was deliberately decided not to recruit researchers from the R2N consortium itself. The contact was successful in most cases because we were able to establish a known connection to

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researchers in the requests. We asked the interviewees about other researchers who might be open to a possible interview.

The inclusion criteria were: 1) experience with animal models and/or non-animal models in basic and translational research; 2) the possibility to conduct the interview in English or German; and 3) consent to participate and to the publication of results in an anonymized form. Different career levels (PhD to senior researcher) and various experiences (animal experimentation, alternative methods, or both) were determined as further selection criteria. The end of recruitment was determined by the saturation of content that emerged from the successive analysis of the interviews (see below).

Interview Organization: The interviews were carried out as *episodic interviews* [22], a combination of a *guideline-based/semi-structured interview* with a predetermined order of (open-ended) questions and a *narrative interview* that aims to incite narratives on the experience of deciding between animal testing and alternative methods. The interview guide was divided into three parts. The first focused on the individual understanding of what alternative methods are. The second concentrated on specific decision situations, and the third centered on the research environment and other contextual factors.

The interview guide was pretested with bioscientists of the R2N consortium, as they were similar to the desired interviewees in terms of education and experience. The interview guide was slightly revised in terms of wording. The interviews were conducted by telephone in German and recorded with prior consent (primarily by IP, at the first interviews together with MM). The interviews were subsequently transcribed and the resulting texts were analyzed qualitatively. The insights we gained from the interviews are based primarily on individual experiences and personal attitudes. Nevertheless, it is possible that some of the aspects extracted reflect the perspectives of third parties or general attitudes. However, since this distinction is not relevant for the analysis and discussion of the (abstract) reasons, it will not be considered further.

Analysis and categorization: Qualitative content analysis was used to analyze the texts, mainly following the method of Mayring [23]. It is an interpretative analysis method from social science research for processing qualitative data, based on the premise that the analysis starts from everyday processes of understanding and interpreting linguistic material. The method is, thus, based on psychological and linguistic theories of everyday text comprehension.

Qualitative content analysis following Mayring allows the combination of concept- (deductive) and text-driven (inductive) approaches for coding and categorizing text snippets. The concept-driven elements for identifying relevant text snippets and coding them were based on a certain understanding of value judgements and their structure developed within the project, the so-called *Value Judgment Model* (see in detail below). The text-driven code generation was successively reconciled with the more theoretical-driven coding. The codes were then abstracted and paraphrased to condense their content and make them anonymous. MAXQDA software was used to keep track of codes and associated text snippets.

The analysis was conducted step-wise by one author (IP), with interim results discussed repeatedly within the team (HK, MM), so that the code tree evolved continuously. In a further step, the codes were categorized into *reasons for using alternative models* and *reasons for using animal models*, and each was further divided into four categories (mainly based on inductive categorizing): *Personal Attitudes, Work Environment, Animal* and *Scientific*. Each code was assigned an anchor quote from the interviews to help understand the genesis of each code. One author (HK) took the lead on this, with ongoing review by a second author (IP). Finally, the results table was discussed and finalized by all authors (HK, IP, MM).

Theoretical/Ethical Analysis and Evaluation

Value Judgment Model: Since reasons for choosing an animal model or an alternative method always include value judgements (value judgements are part of the reasons or, more broadly, part of the logical reasoning structure), the project needed to elaborate more clearly on the concept of "value judgement" and its role in such decision-making processes. Accordingly, a conceptual model, the *Value Judgment Model*, was developed [19]. This model not only informed the identification and

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coding of the texts resulting from the interviews (see above), but also served the subsequent theoretical/ethical analysis of the empirical results, i.e., the reasons and categories of reasons analyzed in the interviews.

In brief, according to the *Value Judgment Model*, value judgments are the conclusion of an argument that consists of at least one descriptive *premise* (e.g., "The alternative method A has/has not characteristics Z") and at least one evaluative *premise* (e.g., "X is good/bad or right/wrong") (see more in detail [19]). Descriptive premises (assumptions) are characterized by the fact that they, in principle, can be empirically verified. Explaining the evaluative premises (assumptions), which are often only implicitly provided when scientists give reasons for their choices, serves to clarify and confirm the relevant values that are involved. Both premises could be supported by descriptive or evaluative/normative *backings* (e.g., epistemic processes, infrastructure, work environment, interest(s), emotions, desires, needs, and further or "higher" values or ethical principles). These considerations are less present or conscious, but can influence reasoning and, thus, decision-making processes.

Ethical framework for animal research ethics: The *Value Judgment Model* makes it possible to (better) identify value judgments in texts where reasons are given, and reveal (or reconstruct) their justificatory role when such reasons are given. However, the model is not intended to evaluate reasons from an ethical perspective. This requires an ethical framework.

In order to evaluate and reflect on the reasons identified (HK and MM), an established so-called principlism approach [24] to bioethics was used. Such approaches use mid-level ethical principles (abstract norms) to identify, analyze and ultimately evaluate actions. However, these principles are not in a predefined hierarchical order; which principle has the most weight in a particular case – and the duty to be followed – depends on the context and particularities of that case, as well as on the concrete analysis and subsequent argumentation.

Different principlism approaches have also been developed for different areas of bioethics. The *animal research ethics* approach [25] can be used for questions related to animal experimentation. According to this approach, the suffering of laboratory animals can only be justified if it is absolutely necessary (*Principle of No Alternative Method*), experiments may only be as severe as necessary (*Principle of No Unnecessary Harm*), and harm done to animals cannot be unlimited (*Principle of Upper Limits to Harm*). Moreover, basic care must be guaranteed at all time, which also means during the actual experiment (*Principle of Basic Needs*). Furthermore, it is to be expected that benefits (for humans) and harms (for animals) have to be weighed against each other, both by the researchers themselves and the respective responsible commissions; it is required that the benefit is sufficiently high to be able to justify any harm to animals at all (*Principle of Sufficient Value to Justify Harm* and *Principle of Expected Net Benefit*). The approach explicitly does not aim to replace the established "3Rs" (Replacement, Reduction and Refinement [26]), "but to add complementary content for animal research ethics that the 3 Rs framework fails to provide" [25] (p. 310). In addition to this approach, the importance of maintaining/upholding scientific validity in animal experiments [4,26] as well as scientific integrity [27] can be emphasized as additional ethical principles.

3. Results

We contacted 30 potential interviewees (including follow-up) and conducted 13 interviews between March and June 2020 (four people declined the request and 13 did not respond to our invitation). Further characteristics of the interviewees can be found in Table 1.

In the following, we will give an overview of the results of the interviews: firstly of the understanding of alternative methods, secondly, regarding the spectrum of all the reasons identified for the use of animal or alternative models. Additionally, some of the reasons are evaluated ethically. Thereby, we will only take up a part of the reasons identified to illustrate relevant ethical aspects.

Table 1. Characteristics of the experts interviewed.

Characteristics	Sample (n = 13)
Gender (woman/man)	31 % women

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Age (< 30, 40–50, > 50)	8 %, 46 %, 46 % (respectively)
Level of expertise (junior/ senior)	62 % senior researcher
Length of interview (min)	20 to 46, mean 32

What is understood by "alternative"?

The interviews indicate that there does not seem to be a consistent definition of the term "alternatives." What researchers understand by "alternatives" was answered very differently. Some define it by means of concrete methods: "So, a cell culture experiment would be an alternative for me" (original statement from an interview transcript: Interview 9). There is often a very specific understanding of what an alternative is. This leads to the fact that the perspectives refer to very specific contexts and are only transferable to a limited extent. Some researchers defined alternatives with the help of the 3Rs concept: "For me, alternative methods are methods that do not require animal material and completely replace an animal experiment or part of an animal experiment" (Interview 8). In this case, "alternative" is also understood as a completely *animal-free* alternative, where animal products (e.g., blood, enzymes) are no longer required, for example, as a nutrient solution. However, this understanding was not necessarily shared when referring to the 3Rs, as which of the latter was used for the understanding was different: "Well, I would understand alternative methods to be techniques in which, on the one hand, the stress that occurs within animal experiments / to which the animals are exposed can be reduced. And, on the other hand, animal experiments can be totally replaced as a whole" (Interview 1).

Others referred to the definition of an animal experiment from the German Animal Welfare Act [9] and derived their definition of alternatives from it: "For me, animal testing alternatives would actually mean that no animal is used in the sense of an animal test" (Interview 3). However, it becomes clear that there do seem to be any fixed boundaries regarding what counts as an alternative and what does not. Thus, in the discussion about animal experiments and alternatives, it is worthwhile determining more precisely what is actually being talked about, especially when the discussion is not only conducted within the research community but also with a broader public.

What is the spectrum of reasons?

There were 846 passages coded from which 66 specific considerations related to the choice of a disease model were derived. Numerous reasons were given for both the choice of the alternative (39; 59 %) and the animal model (27; 41 %). In both sub-spectra, the reasons are distributed across four areas, with the *Working Environment (WE)* accounting for the largest share (45/37 %), closely followed by *Science (S)* (29/37 %). The areas *Personal Attitudes (PA)* (12/22 %) and *Animal (A)* (7/4 %) are quantitatively smaller. All 66 reasons identified are listed in Table 2.

Additional subcategories were introduced for *Working Environment* (Reasons Concerning Work Organization; Research Climate within Institution; Expert Opinion and Research Funding; Peer-group/ Scientific community; Education and Teaching; Society; Technical Development) and for *Science* (Research Questions and Approaches; Results; Translation/Usability; Publications) because these two areas cover a wide range of topics. Exemplary statements from the original interview transcripts are assigned to all 66 reasons identified in an overview as supplementary material (Table Sup1). The paraphrased reasons are often based on several original statements, only one of which is shown in Table Sub1 for illustrative purposes.

Table 2. 66 reasons why peoples choose an alternative or animal model.

Area of reasons	I choose the *alternative* because …	I choose the *animal model* because …:
Personal Attitudes (PA)	PA1.1: "I am curious to try new things" PA1.2: "it draws (media) attention"	PA2.1: "It can be justified and ethically acceptable" PA2.2: "I will/must comply with the 'state of the art' (animal experiments)"

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	PA1.3: "experiments with animals are stressing me emotionally/psychologically"	PA2.3: "I find it important to carry out experiments again myself and, thus, confirm known results"
	PA1.4: "animal experiments (in this field) were cruel"	PA2.4: "protecting a human being from ineffective or harmful drugs is a higher value than refraining from animal experiments"
	PA1.5: "I want to contribute to change the current practice in research and development"	PA2.5: "I lack confidence in the potential of alternatives"
		PA2.6: "I feel that this is my responsibility in the education of veterinarians
Work Environment (WE)	***Reasons Concerning Work Organization***	
	WE1.1: "alternatives are cheaper"	WE2.1: "there are too many research ethics and legal requirements for research on humans or human tissue"
	WE1.2: "alternatives are associated with smaller amounts of lengthy bureaucracy (e.g., no approval procedure)"	WE2.2: "the development of alternatives is longsome and inadequately funded (while animal experiments are established)"
	WE1.3: "alternatives can be realized more quickly"	WE2.3: "alternatives are often more expensive than an animal experiment"
	WE1.4: "there is suitable infrastructure on site"	
	WE1.5: "I am not authorized and/or qualified to conduct animal experiments"	
	WE1.6: "animal keeping is quite costly"	
	WE1.7: "we never would have been able to do that quantity of tests on animals"	
	WE1.8: "I get more freedom (in choosing experimental design, methods) than in animal experiments"	
	Research Climate within Institution	
	WE1.9: "superiors are demanding or are explicitly supporting the use of alternative methods"	WE2.4 "my supervisor has decided so"
	Expert Opinion and Research Funding	
	WE1.10: "funding lines exist exclusively for them"	WE2.5: "reviewers tend to come from a generation in which animal experiments are recognized above all"
	WE1.11: "it can be used to answer the now wider-ranging and more complex research questions"	
	WE1.12: "reviewers respond in a constructive manner"	
	WE1.13: "I was contacted by agencies/research funders to use (test, develop) alternatives"	
	WE1.10: "funding lines exist exclusively for them"	
	WE1.11: "it can be used to answer the now wider-ranging and more complex research questions"	
	WE1.12: "reviewers respond in a constructive manner"	
	WE1.13: "I was contacted by agencies/research funders to use (test, develop) alternatives"	
	Peer Group/ Scientific Community	

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	WE1.14: "I have already internalized the 3R and am, therefore, more receptive to associated innovations"	WE2.6: "science has 50 to 60 years of experience with certain animal models"
	WE1.15: "alternatives have, in the meantime, been accepted by the community"	
	Education and Teaching	
	WE1.16: "I would like to reduce the number of animals required for educational purposes"	WE2.7: "there is some content that simply could not be communicated without the direct use of animals"
		WE2.8: "animal experiments are legally part of the training of veterinarians; it is written in the license to practice and, therefore, mandatory"
	Society	
	WE1.17: "society is demanding more alternatives and animal experiments are respectively more criticized than in the past"	---
	Technical Development	
	WE1.18: "new technology (e.g., CRISPR/Cas, IPSC) is enabling me to work in a more targeted manner on a genetic level than working with animal models (e.g., mice)"	WE2.9: "alternative methods are not yet fully developed in my field"
		WE2.10: "I can't (yet) connect the correspondences of the organs/functions in alternatives (so I can't test complex interactions)"
	WE1.19: "I have learned about their many uses through previous experiments with alternatives"	
	Animal Welfare/Dignity	
Animal (A)	A1.1: "I 1: "I want to avoid animal suffering"	A2.1: "they are necessary and before someone does it who doesn't care about animals. I prefer to do it myself"
	A1.2: "it enables various pre-experiments that can avoid animal experiments which otherwise would have to occur"	
	A1.3: "The consequences of a failed experiment are much less critical than in animal experiments (especially regarding the animal)"	
	Research Questions and Approaches	
Science (S)	S1.1: "a correct replication of the disease or (e.g., cellular) processes cannot be obtained through the animal model (e.g., mouse)"	S2.1: "experiments on living animals rather allow one to discover completely new (unexpected) things"
	S1.2: "I can have a greater degree of control (manipulability) over the experiment"	S2.2: "complex questions/interactions can only be investigated in the whole organism"
	S1.3: "I can preselect (narrow down) substances this way"	S2.3: "I perform research in animals for animals of their species (veterinary medicine), which is very difficult to replace with alternative methods"
	S1.4: "I can better describe and/or explain the basic effects/mechanisms here"	S2.4: "to gain access to and expertise in a disease from it"
	S1.5: "I find the transferability of animal models to humans inadequate"	
	S1.6: "I can get results without hypotheses"	

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S1.7: "I only want to observe a certain step/function (e.g., effector function of T cells against tumors) and not the whole process (as would occur in an animal)"	
Results	
S1.8: "the standardizability of the experiment is higher (more valid and reproducible results)"	S2.5: "alternatives currently produce too many false-positive or false-negative results"
S1.9: "it allows me to avoid variability between individual animals"	
S1.10: "conditions of animal keeping in the laboratory can distort the results of animal experiments, and some of these effects are unknown"	
Translation/Usability	
S1.11: "it is now increasingly possible to obtain approval for new experimental therapeutic approaches without prior animal testing"	S2.6: "the industry often demands results from animal models, and otherwise commercialization of our results is hardly possible"
	S2.7: "the results of alternatives (alone) are an insufficient basis for clinical studies with humans (translation)"
	S2.8: "it is a test method recognized by the OECD in safety assessment" (TOX)
	S2.9: "there are also legal requirements that prescribe some animal experiments"
Publications	
S1.12: "I get publishable results faster when I am using an alternative"	S2.10: "because with alternatives you have a hard time with some important journals"

The (qualitative) spectrum indicates what reasons can, in fact, play a role, at least in the reconstruction in the first-person perspective and regarding (possibly subsequent) questions of justification. Nevertheless, they are not effective everywhere and all the time, or endorsed by all researchers. It does, however, provide an overview that can be used to systematically select significant aspects from an ethical perspective.

What are exemplary ethical dimensions of the reasons?

Personal attitudes: Based on the (current) societal norm setting, which basically allows animal experiments, robust ethical principles and a defined procedure for third party approval (competent authorities) are safeguards for ethically defensible research involving animals.

Knowing these safeguards may be enough for some researchers. They may not need to think any further. In that sense, saying "I choose the animal model because it can be justified and ethically acceptable" (PA2.1, Tab. 2) could imply a reference to a general attitude to "delegate" the decision to a "higher" level of decision-making. For others, emotions play a stronger role, for example, "I choose the alternatives because experiments with animals are stressing me emotionally/psychologically" (PA1.3). *Ethical dimensions:* None of these personal attitudes is *prima facie* ethically better or worse. Instead, they are expressions of different implicit assumptions. Following the *Value Judgment Model*, descriptive *premises*, such as "*the established approval procedure is most likely to lead to a 'correct' decision about moral permissibility*" (even though others may disagree), or "*my active role and the suffering I am directly confronted with affect me too much personally*," can be rationally reconstructed from the interviews. The latter example also implies an evaluative *backing* that suffering (in general or

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specifically also regarding animals) is ethically not good – otherwise it would not be experienced as emotionally burdensome.

Furthermore, personal attitudes are grounded in a) *values/principles* ("protecting a human being from ineffective or harmful drugs is a higher value than refraining from animal experiments," PA2.4), b) *emotions* (PA1.3 see above) or c) *interests* ("I am curious to try new things,", PA1.1). *Ethical dimensions*: Such personal attitudes are legitimate for any person. They cannot, however, serve well as *impersonal normative justifications* (claiming to give intersubjective comprehensible reasons for the rightness or wrongness of an action) but only as *personal justifications* (claiming only to state why this particular person has judged a particular action to be right or wrong and/or has preferred it or refrained from it) (cf. [28]). This is because, for example, emotions or desires are not generalizable, nor are personal experiences or personality structures and associated interests. However, some issues should be discussed from an ethical perspective. These considerations are referred to as *secondary interests* in the concept of conflicts of interest in the professional context. It is important to note that primary and secondary interests are often not in conflict with each other, but can even have positive effects (personal curiosity of a scientist). However, if they are conflicting with *primary interests* (e.g., the pursuit to produce relevant and valid findings or adherence to the six principles of animal research ethics), they should not influence the professional judgement inappropriately [29]. This could violate a general norm of objectivity or *disinterestedness* (as expressed, for example, in the Mertonian norms/ethos of science [30]). In addition, if someone argues that conducting animal experiments stresses them emotionally, this probably (implicitly) refers to a general/abstract moral norm, such as 'do not harm others' or 'thou shalt not kill.' These norms are presumably shared by significantly more people than the (fictitious) motivation of "striving for media attention," which would primarily satisfy a personal need.

In sum, personal attitudes influence decision-making (such as on a disease model) or our positions towards certain professional issues (e.g., conflict of interest issues or scientific integrity). As an interpretation/reconstruction, for example, on the basis of the *Value Judgment Model*, suggests, it is necessary in each case to examine whether emotions (but perhaps also interests) are based on general and consensual moral norms that appear as implicit evaluative backings. In such cases, however, the norms should be brought into focus because they allow for an impersonal normative justification. Therefore, it is ethically important to look at the further justifications ("argumentative backings") of such seemingly purely personal attitudes.

Work environment: Some scientists argue that "alternatives are associated with smaller amounts of lengthy bureaucracy (e.g., no approval procedure)" (WE1.2). *Ethical dimensions*: The evaluative assumption (and, thus, premise in the justification structure) behind this might be that "lengthy bureaucratic processes are bad for / are a hindrance to research." It should be noted that this is a specific perspective that emphasizes *efficiency*, which can be understood as a shared value or (ethical) principle in science, and especially in research within the health-care system (given that public resources are being spent). However, in the research context, the scientific validity of the findings or the ethical integrity of the scientific project is probably more important than efficiency, i.e., a higher value must be placed on validity or integrity in a weighing process. This does not mean that efficiency cannot be taken into account, but decisions should not be made only *in favor* of efficiency (and against, for example, validity) – choosing an alternative method only because it means less bureaucratic effort would be ethically questionable as long as validity and integrity requirements are not sufficiently fulfilled. After all, bureaucracy, however burdensome, is not an end in itself but a best practice to ensure the validity and integrity of research.

Other aspects of the work environment can also play a role in the choice of a disease model. Some researchers, for example, report that "superiors are demanding or are explicitly supporting the use of alternative methods" (WE1-9) or "my supervisor has decided so" (WE2.4). *Ethical dimensions*: There is a mutual dependence or dependent relationships in academia (as well as in private sector). It is important to be aware of these and their possible influence on our decisions via the definition or modification of descriptive assumptions or, above all, evaluative assumptions (and the values behind them). This is important because conflicts can arise between one's own evaluative assumptions and

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those decisions and actions that one must follow or support as a team member. In extreme cases, this can lead to moral distress, a feeling of helplessness that what one feels to be ethically right is not being done, and that one cannot (adequately) influence this due to hierarchies.

A further important context factor that was brought up in the spectrum of reasons is the relevance of available or necessary infrastructure (WE1.4 and WE2.2-3). If animal laboratories and related expertise are already available, and the switch to an alternative method is, therefore, assumed to be too costly, this may influence the decision. Conversely, researchers who only work *in vitro*, for example, will have neither the infrastructure nor expertise for animal research, and if they do want to resort to animal experiments, they will have to outsource them (e.g., via cooperation partners) (WE1.5, Interview 10). *Ethical dimensions*: Similar to bureaucratic requirements, actions based on existing or required infrastructure do not necessarily violate an ethical principle. Again, however, it would become ethically problematic if scientific validity or integrity were negatively influenced, or, in extreme cases, if animal experiments were carried out that were, strictly speaking, not absolutely necessary (*Principle of No Alternative Method*) – simply because the infrastructure would only allow animal experiments to be performed.

Science: Statements belonging to this part of the spectrum of reasons are always specific to a field of research. This means that for statements such as "I find the transferability of animal models to humans inadequate" (S1.5) or "I lack confidence in the potential of alternatives" (A2.5), a "related to my research field XY" should be added in the mind. This contextualization becomes clear in statements such as "complex questions/interactions can only be investigated in the whole organism" (S2.2), which seems to be more obvious in some fields than others. *Ethical dimensions*: Such an assumption forms, more or less directly, the descriptive premise in the justification of an animal experiment, likely to be combined with an evaluative premise based on the *Principle of No Alternative Method*. (In the theory of principlism, it is also conceivable that the *Principle of No Alternative Method* is *specified* accordingly on the basis of this descriptive information, so that it says, for example: "If no alternative methods are available or suitable for studying complex issues or interactions in the whole organism, then, *prima facie*, an animal experiment may be carried out.")

Other researchers argue that (regarding their research field): "I get publishable results faster when I am using an alternative" (S1.12). *Ethical dimensions*: At first glance, this does not seem so ethically significant. However, if one considers the fact that only published findings can fulfill the central promise of generating value through research, this can be a descriptive premise relevant for respecting the *Principle of Sufficient Value to Justify Harm* (though it is not sufficient to fulfill it).

In contrast to such examples of reasons that can be attributed more or less directly to justifications using ethical principles, there are *pragmatic* considerations, especially regarding the usability of the results. *Ethical dimensions*: A researcher's interest or need to commercialize their work is initially legitimate ("the industry often demands results from animal models, and otherwise commercialization of our results is hardly possible," S2.6).

We further extracted the argument that some researchers continue to work in basic and translational research with animal models because "science has 50 to 60 years of experience with certain animal models" (WE2.6). *Ethical dimensions*: The plausible descriptive premise is that there is a lot of experience and achievement with these animal models that have helped to advance science. Whether these benefits exist and, if yes, what their magnitude is, has to be addressed very field-specifically and should be documented in a comprehensible and systematic manner. If this is based more on financial considerations (e.g., avoiding the need to invest in infrastructure), this is more problematic from an ethical point of view (probably violating the *Principle of No Alternative Method* and *Principle of No Unnecessary Harm*). In specific fields and to a certain extent, there may be legitimate reasons why a more suitable model cannot be implemented in a specific situation, i.e., does not represent the "best choice." However, scientific factors and animal welfare should usually be decisive.

Another issue that should be discussed is that both animal models and alternatives "imitate the human organism only to a limited extent" (S1.1+5 and S2.7). We should be clear what kind and scale of uncertainties we want to accept when going from preclinical to clinical research and, thus, begin

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to involve humans. Do these uncertainties tend to be larger, equal or smaller for alternative models? Perhaps this premise is wrong because these uncertainties related to the use of alternative methods impress more that the common and known uncertainties in animal models. Finding a clear answer to this question is not made any easier by the replication crisis (e.g., [31,32]) and biases in the risk assessment based on investigator brochures [33,34]. *Ethical dimensions*: From an ethical point of view, it concerns the meaningfulness and the (social) benefit, which must be empirically proven and critically reflected on a field-specific basis (*Principle of Expected Net Benefit* and *Principle of No Unnecessary Harm)*. Against the background of dynamic technological developments (e.g., new opportunities through artificial intelligence), this should be done on an ongoing basis.

Researchers have to continually find *sources of funding* and, thereby, orient themselves to the external (public) research funders. Great investment into new technology and the qualification of personnel to use it is currently required for a shift more towards alternative methods, and if the investment costs are funded, this is beneficial (WE1.10+13). *Ethical dimensions*: This is not part of a sound justification. There is hardly any evaluative descriptive premise that would be sufficiently credible – from an ethical perspective – to justify the conclusion (thus, the value judgement) that 'The animal experiment is the better choice.' An evaluative premise, such as 'It is good/right to conduct an animal experiment (at least better than not conducting any research) if an alternative is generally available but cannot be adequately funded in this case,' may be the one that formally enables justification. However, it obviously opens up countless exceptions to the *Principle of No Alternative Method*, which is a quite uncontroversial and also, as mentioned in the introduction, legally defended. Briefly, it does not make the use of animal experiments "more right" *if* alternatives were available or could conceivably be developed but neither are sufficiently paid for. However, with reference to the *ought-implies-can principle* (simplified: one can only demand normatively what is also realistically realizable) (e.g., [35]), it could be argued that animals are *the only possible disease model* in this case. Nevertheless, whether the specified ethical principle following the *Principle of No Alternative Method* would then not have to be "no animal experiment if an alternative is available but financially unfeasible" must be examined in each individual case (e.g., to what extent is the alternative available but not available, to what extent would it be suitable).

Animal welfare: All reasons that are subsumed under this category in the spectrum of reasons are either easily complemented by principles of animal research ethics (when the reasons are referring to descriptive assumptions) or are, in the end, specifications of these principles (e.g., "thereby allowing various pre-experiments that may otherwise cause animal experiments" (A1.2), *Principle of No Unnecessary* Harm and *Principle of Sufficient Value to Justify Harm)*. Given these principles, current (animal protection) laws, and social and political movements that aim to improve animal welfare (or even rights), it must be a guiding consideration in decisions. *Ethical dimensions*: It is especially difficult to argue why animal welfare should be restricted in favor of mere pragmatic contextual factors – all the more so when an ethical stance is taken that always gives priority to the *moral point of view* or the *moral position* over other points of view, especially self-interest (e.g., [36,37]). Therefore, this only seems possible where pragmatic reasons can refer to ethical values and principles in their argumentative backings. However, as shown by way of the example above, this will seldom occur. Even if it does, whether the weighing up between different ethical values or principles is convincing must then also be examined again. By contrast, defined constraints are conceivable in favor of scientific considerations (e.g., validity) and their related ethical values (e.g., social benefit), whereby the appropriateness must always be checked in a review process by third parties.

4. Discussion

We empirically identified a spectrum of 66 reasons for choosing an alternative method or an animal experiment in basic and translational research. The largest quantitative share is accounted for reasons that can be derived from the work environment (> 37 %) and the scientific context (> 29 %). Although this does not imply a conclusion about the legitimacy or relevance of the arguments, it is noteworthy that such reasons receive less attention in the ethical debate, which tends to focus immediately on well-known issues of animal or research ethics. Thus, while some ethicists may,

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therefore, argue that only principles that deal with the animal and the necessity of its use in a laboratory are allowed in ethical decision-making, it seems important to understand reality and accept the actors' scope of action and motivations as an empirical fact. Nevertheless, it is not surprising that some reasons in the spectrum can also be more or less directly associated with basic animal and research ethics principles (e.g., protection of non-human and/or human animals). In this context, however, more general values and principles were also reconstructed as a normative reference (e.g., "thou shalt not kill"). In addition to the value-based reasons, others were more pragmatic and argued with, for example, infrastructure or funding. From an ethical perspective, they may not be equivalent, but they can represent hard constraints in reality and must, therefore, be considered. Moreover, personal attitudes were identified as relevant for the decision-making, albeit not necessarily for impersonal (intersubjective) normative justification. For the latter, it is important that personal attitudes are congruent with commonly agreed values and that effective measures are taken to promote professional ethical conduct. It must also be acknowledged that there are (legitimate) secondary interests that can influence professional judgments. The *personal (secondary) interest*, for example, not to attract attention ("society demands more alternatives or animal experiments are criticized more than before," WE1.17) versus the *professional (primary) interest* to generate relevant valid findings ("the modes of action can only be studied in the intact organism or in the whole organism," S2.2). As it is difficult to identify illegitimate influences on professional judgment (blind spots), however, it may be helpful to think systematically about particular reasons or considerations. We hypothesize that the pragmatic reasons, which might often have an influence on the decision, are not reflected so much ethically because they are not perceived as "ethical" or "ethically relevant" (since they do not directly violate ethical principles). Only the clarification that these reasons may indirectly correspond to ethical principles or contradict them would also enable a more reflected decision-making.

There is a *generation of researchers* who have worked without new technologies (e.g., artificial intelligence) for many years and have based their academic careers on animal models. It would be wrong to imply that this generation is more critical of new technology overall, but this impression was described for individual cases in the interviews ("Reviewers tend to come from a generation in which animal experiments are recognized above all," WE2.5). It is perhaps not yet imaginable to be able to understand complex things in an life form without being able to grasp them in a living organism. Virtual and organic replicas of reality or information-processing computer systems, however, make ever-greater demands on the justification of the necessity of particular animal models. In this discussion, fundamental value questions also play a role (e.g., outcomes, results and interpretation, dealing with uncertainties).

In general, reasons cannot be simply observed, but are only accessible through qualitative analysis in a reconstructed way. Thus, by acknowledging that decision-making in specific research areas refers to individual cases, specific decisions are not reproduced one-to-one in this paper. Nevertheless, this spectrum provides a framework for reflection on individual behavior and may help to make one's own perspective in the ethically tense field of basic and translational research more conscious and stronger. The analysis has shown that it is important and valuable to distinguish between descriptive and evaluative premises and other elements of justification (backings). Within the descriptive and evaluative premises, it is again useful to distinguish whether they are, for example, statements about, for example, infrastructure, financing, harms or benefits, or statements expressing things such as emotions, interests or needs. While one can use the Value Judgment Model analytically for this purpose, in practice it will probably suffice to make it clearer that there will always be at least one descriptive and one evaluative premise justifying the value judgment in relation to a disease model. Being clear about this, and especially trying to make the evaluative premises more explicit, can help to check whether the value judgment is sufficiently supported. The tendency in the natural sciences may often be to secure the descriptive side as evidence-based as possible, but to forget which value-related premises are already implicitly assumed in order to make a value judgment.

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The challenges in the recruitment phase were essentially overcome by a change in strategy and some additional efforts. However, it was not possible to include researchers at an early stage of their career (PhD), and it cannot be excluded that relevant aspects were overlooked as a result. However, the interviewees also reported on the beginning of their careers, which could count as retroactive consideration.

5. Conclusions

A wide range of reasons could be identified empirically, and ethical frameworks were useful to systematically address the ethical dimensions, mainly those of animal research ethics. Regarding the ethical analysis, the reasons were then reconstructed into relevant descriptive and evaluative premises according to a Value Judgement Model [19]. All considerations in ethical decision-making have to be weighed against each other and accordingly balanced in a conclusion. Thereby, considerations based on generally accepted values, such as the principle of not harming or killing, should be assumed to be of fundamental importance ("ethically superior"). Such values should be given more weight than, for example, the desire to gain media attention. This demonstrates that the quality of the reasons and not the quantity is important in the weighing process. The weight we give to a particular consideration in the decision-making process also depends on the certainty accompanying it. However, the central moral problem consists of the conflict between *animal welfare* and *social benefit* when using animals in biomedical research (e.g., [25]). There are serious ethical arguments on both sides in this classic ethical dilemma. This means that the rejection of alternatives can also have an ethical justification (e.g., "protecting humans from ineffective or harmful drugs is a higher value than not using animal models," PA2.4).

Researchers should be supported in the decision-making process because there are various aspects to be considered in balancing (all aspects relevant and more or less legitimate reasons could be involved). First of all, this means raising the awareness of decision-making situations. Even if it sometimes seems that everything is predetermined, decisions are always being made about a particular model in a specific project, about the strategic engagement with a new model/technology, or even about the long-term orientation of a research team (i.e., whether or not the team intensifies the usage or development of alternative methods). Appropriate measures to support conscious decision-making range from documentation sheets for ethical decision-making to training courses and institutionalized ethics counselling. There are also many dependencies in science (e.g., young scientists towards not only senior researchers, but also funders). This results in power structures that should not be a burden for ethical decision-making or a slowdown of further development.

Currently and in the mid-term, however, no disease model represents the human life form in the same way as the real human organism. As long as animal experimentation is not prohibited in principle (and decision-making is, therefore, unnecessary), this means that researchers rely on various *value judgements* that are at stake and should refer to *broadly accepted criteria* for choosing a disease model.

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