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Prof.dr.ir. J.-B. Prins

Animal welfare: who cares?



**Universiteit
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Animal welfare: who cares?

Inaugural lecture by

Prof.dr.ir. J.-B. Prins

on the acceptance of his position as professor of

Laboratory Animal Science

at the Universiteit Leiden

on Friday May 12, 2017



**Universiteit
Leiden**

The Netherlands

Mister Rector, members of the Board of the LUMC, esteemed colleagues, dear listeners,

Introduction

“Animal welfare: who cares?”

In the context of laboratory animals, the short answer to this question: “don’t we all?”, is certainly not the whole answer.

It would be the easiest answer, of course, because then we could all go straight to the bar.

But the answer to this question really depends on who you ask. Amongst yourselves, there will be critical and less critical noises when it comes to utility and necessity of scientific experiments with animals and how that relates to maximum protection of animal welfare.

I could have used press pads to gauge the mood in the hall, but an inaugural lecture is not the place for that.

As it happens, I’m already familiar with the viewpoints of a number of you. So I know that the whole spectrum is represented here this afternoon.

I leave it to you to find a place in that spectrum for the long answer I’m going to give you today.

During this public lecture, I want to tell you about the state of affairs of the “dossier on scientific procedures on animals” in the Netherlands and in Europe. For the people who are more up-to-date on the subject, please see this as my invitation to you to accept shared responsibility for the animals that we use to conduct research into the health of humans and their surroundings, and convert it into targeted action, where necessary.

By shared responsibility I really do mean shared: the researcher, the laboratory animal scientist, the administrator, the Government, the politicians, industry in general and the pharmaceutical industry in particular, and of course the public

in its capacity as critical citizens but also in its capacity as citizens who benefit from the accomplishments of science and technology on a daily basis.

In April 2016, State Secretary Van Dam of Economic Affairs contacted the National Committee for the Protection of Animals used for Scientific Purposes, also called NCad,¹ to ask for advice on how we can help the Netherlands become a global leader in animal-free innovation by 2025. The subject of that request was entitled: “phasing-out schedule”. The State Secretary made this request not in a fit of moral integrity, but motivated by the international and national social and scientific debate around the use of animals for research, and by the report of the Think Tank for Additional Financing Alternatives for Scientific Procedures on Animals [in Dutch: Denktank Aanvullende Financiering alternatieven voor dierproeven].¹

As a member of the NCad, I have to confess that the State Secretary’s request caught me off guard - not just because the subject was “phasing-out schedule”, but also because the deadline by which the State Secretary expected an answer from the NCad was before the end of 2016.

The fact that I was caught off guard isn’t so important, but you can imagine how the various parties involved in scientific procedures on animals, including the representatives of the (bio)medical research field, the pharmaceutical industry and organisations such as the Dutch Society for the Replacement of Animal Testing (Proefdiervrij) and the EDEV Foundation (Een Dier een Vriend), each reacted from their different perspectives. With mixed feelings, I would imagine: from scepticism to pleasant surprise.

A transition to animal-free research and its translation in the Agenda Animal free Innovations is comparable to the transition currently taking place in the energy sector - the energy transition - from fossil fuels to renewable energy, particularly wind and solar energy. A transition to which the various stakeholders have committed themselves by signing the energy agreement.¹¹

We had just had a revision of the Experiments on Animals Act in late 2014.² A revision based on the 2010 European Directive for the protection of animals used for scientific research.³ A revision that resulted in many changes for conducting research with animals. And now yet another step further.

In Europe, the 2010 Directive was under attack from a Citizen Initiative with more than 1.1 million signatures from EU citizens.^{III} This Citizen Initiative, which European legislation made possible to enable residents in the EU to hold EU legislation up for debate by means of more or less direct democracy, asked for that Directive to be replaced with a ban on the use of laboratory animals. The European Commission has processed this Citizen Initiative and has rejected it.^{IV} At the same time the Commission referred to the review of the Directive in the second half of 2017. One of the European Commission's responses was to organise a scientific conference last December, with the title: "Non-animal approaches - the way forward".⁴

The aim of the conference was to hold a dialogue with the research community on how the progress made in science and technology can best be used to develop and validate animal-free techniques that could ultimately lead to animal-free research practices. Very similar to and in line with what the State Secretary wants.

Prof. Staal and Mummery of the LUMC were invited to speak at that European scientific conference. Prof. Staal made it clear that even with existing research practices the decision to go for an animal experiment (procedure) is not always as obvious as it might seem. Prof. Mummery illustrated how a combination of technological developments and biomedical scientific discoveries are leading to animal-free innovations.

Trade-offs, challenges and opportunities voiced by LUMC members, leading researchers in their specialist fields who showed with their contributions that animal testing isn't self-evident - amongst other things, by bringing together various disciplines so that innovations are given a better chance. At the

same time indicating that scientific procedures on animals are still an indispensable part of (bio)medical research.

Last December, the NCad submitted its advice, "Transition to animal-free research", to State Secretary Van Dam. I'd have liked to show you the short video that was made for that occasion, but once again an inaugural lecture is not the place for that. In under 4 minutes, this video very clearly illustrates the crucial questions and dilemmas. You can find the video on the NCad's website. I recommend that you watch it. An English-language version is now also available.

There are many dilemmas when deciding whether or not to use animal testing.

All animal testing involves weighing of the pros and cons of the suffering - or, a term often regarded as euphemistic, the hardship - that we put the animals through for the expected yield of the research, but this kind of comparative assessment is not easy to make.

Is it really possible to perform an objective prospective welfare assessment? And how does one assess the benefit(s) of the experimental outcomes?

And then there's the question of whether methods that don't use animal testing counterbalance what is also called the "golden standard", i.e. animal testing. While at the same time, it's obvious that not all results achieved with scientific procedures on animals can be translated to humans. The argument against this is that it is often due to the choice of animal models rather than to the models themselves.

With all the conflicting opinions and interests, the animal testing issue soon falls into the category of "wicked problems". Which means that it really involves an issue that's difficult if not impossible to resolve because of the incomplete, conflicting and changing requirements that are often difficult to recognise.

In the end, which advice did the NCad give the State Secretary about how to turn the Netherlands into a global leader in animal-free innovation by 2025?

In its advice, as far as the possibilities and the intended time schedule for replacing scientific procedures on animals are concerned, NCad makes a distinction between roughly two types of research: statutory safety and toxicity research, and fundamental and translational research, which is research aimed at enhancing our knowledge and understanding of biological processes, for example, and translating it to humans or animals. The majority of the research conducted at the LUMC and at Leiden University must be included in the category of fundamental and translational research.

The NCad then comes to the conclusion that the transition to animal-free innovation applies to all types of research, but that in reality that transition will take place at different speeds. For the research required by law, the transition to methods that don't use animal testing within ten years is more realistic than for fundamental and translational research. This because the bottleneck to the introduction of animal-free methods in statutory research is not infrequently caused by legal or political barriers and not necessarily because an animal-free method is not available.⁵

Legislation and implementation

Until the revised Experiments on Animals Act came into effect on 18 December 2014, every institution licence-holder had access to or employed a laboratory animal expert. The English term actually describes his/her job much more accurately: Laboratory Animal Welfare Officer. This expert has now been replaced by the Animal Welfare Body. Every institutional licence-holder now has its own animal welfare body or has access to one. The animal welfare body has taken over the tasks of the laboratory animal expert, while ex-laboratory animal experts have been appointed as chairpersons of the Animal Welfare Bodies. This means that their expertise has stayed where it belongs, namely in the animal welfare body.

Due to that transfer of tasks from one expert to a team of experts with knowledge in the field of scientific procedures on animals and laboratory animals and their welfare, as well as representatives of other scientific disciplines and the

availability of laboratory animal medicine expertise, we can rightly say that when the revised Experiments on Animals Act came into effect, stricter requirements were defined for the internal organisation related to animal testing and laboratory animals.

The animal welfare body as the “laboratory animal partner” in research that uses animals.

That raises expectations and creates obligations... “noblesse oblige”, as one of my esteemed colleagues might say.

I've noticed that since the revised Experiments on Animals Act came into effect in late 2014, the statutory range of tasks of the animal welfare body, which is already extensive, is continually being expanded with tasks that keep turning up on the job - tasks for which it's apparently easy to say: “oh, the animal welfare body can do that”. Because of this, the responsibilities of the animal welfare body are increasing all the time. So the staffing and organisational structure of the Animal Welfare Bodies will have to keep pace with that. At the same time, some restraint should be shown when it comes to allocating even more tasks to the animal welfare body. We can only hope that this is a temporary bottleneck, one of the teething problems in the “startup phase” of the revised Experiments on Animals Act.

As the representative of the Animal Welfare Bodies and their point of contact, the Animal Welfare Body platform should play a defining if not a leading role in solving this and other urgent matters. I hope and assume that this will soon be the case.

In late 2014, the Dutch Government in The Hague had to quickly initiate the organisation and implementation of the system for obtaining project permits to set up and implement scientific procedures on animals. To do this, it had to use existing organisational units such as Animal Experiment Commissions (DECs), and set up several new organisational units, such as the Central Authority for Scientific Procedures on Animals - the CCD.^v The European Directive, on which our revised Experiments on Animals Act is based, makes it possible to set up a project permit system that both protects the welfare

of animals and complies with an important condition for carrying out ground-breaking, trend-setting, and competitive (bio)medical research, namely flexibility and the ability to respond to new developments relatively quickly.

In the period between 2010 and 2014, consultations with all the organisations concerned - the so-called stakeholder meetings - were initially organised by the Ministry of Public Health, Welfare and Sport and later by the Ministry of Economic Affairs to discuss the draft bill of the revised Act and the related organisational units and their relations to be set up. One proposal met all the requirements of the legislature, society as a whole and the researchers: a real ethical test of a project licence application, implemented centrally by the Central Authority for Scientific Procedures on Animals, in which the researcher has described his strategy for achieving the specified research objective. And then, as part of the licence that was granted, a locally implemented technical assessment by the Animal Welfare Body of a research plan or work protocol of limited scope in which the individual animal test is described in detail. In my opinion, the ethical and technical assessment are not yet sufficiently separated and the process seems to be stagnating in what gives the impression of being a double assessment and a limitation of the options offered by the project licensing system. Because of this, we are denying ourselves the benefits offered by the project licensing system as opposed to the “old” DEC system. We mustn’t make this point more difficult in the Netherlands than Europe has intended it to be. It is important that, in attempting to protect the welfare of animals used for research, we keep asking ourselves: is the welfare of the animal well served by this?

The European Directive holds the promise of a potential win-win situation in which animal welfare and scientific research both benefit. For that to succeed in the Netherlands, it needs the endeavour, cooperation and benevolence of the legislature, the CCD, the DEC’s, the Animal Welfare Bodies, the Institutional Licence holders and the scientists.

Laboratory Animal Science

So, what is the role of the laboratory animal sciences? When taking up his duties as the Netherlands’ first ever professor of Laboratory Animal Science in 1985, prof. Van Zutphen said: “Laboratory Animal Science is developing into an auxiliary discipline of biomedical research”⁶

I know for sure that at the time he meant this in a very positive way.

After all, the research conducted by the laboratory animal scientist is targeted at the animals themselves, with themes such as: animal welfare, behaviour, nutrition, and genetics.

However, I would argue here that Laboratory Animal Science is nothing more, but also nothing less, than an enabler for biomedical research.

Unfortunately, in practice that role is often viewed very differently or is certainly treated differently.

As the most visible exponents of Laboratory Animal Science on the work floor, the former laboratory animal welfare officers were regarded as contributing causes to excessive legal restrictions, too many rules and too much administrative burden. Because of that, their activities were often seen as an obstacle to the progress of biomedical research. That image was reinforced because the research institutes sent them as representatives to meetings on scientific procedures on animals that were also attended by government organisations, policymakers, social organisations and others. They did this with the best intentions, because they were, after all, the top laboratory animal experts in the research institutes. In the institute, they were the personification of everything that made the use of laboratory animals possible - but also made it difficult.

The same applies to the managers of laboratory animal facilities, who, partly due to laws and regulations, lay down rules for access to and use of the facilities, but then add extra rules, albeit with the best intentions. And those extra rules and regulations are often not sufficiently scientifically underpinned and are therefore rightly called into question by users.⁷

So why am I saying that Laboratory Animal Science is an enabler of good science?

To an increasing extent, the scientific literature is critical of the translatability of research results achieved with animal studies to humans, and of the reproducibility of research conducted with animals. More and more, that criticism now appears several times every quarter in the editorials, news and correspondence sections of leading scientific journals such as Nature and Science. Those contributions come up with multiple reasons and give extensive advice on what should be done to improve the translatability and reproducibility of animal experiments or how to replace them.

In a commentary in Nature in 2014 entitled “NIH plans to enhance reproducibility”, Francis Collins, director of the National Institutes of Health (NIH) in the USA, wrote the following about that reproducibility of scientific procedures on animals: “preclinical research, especially work that uses animal models, seems to be the area that is currently most susceptible to reproducibility issues. Many of these failures have simple and practical explanations: different sub-strains of mice and rats being used randomly, different lab environments or subtle changes in protocol. Some irreproducible reports are probably the result of coincidental findings that happen to reach statistical significance, coupled with publication bias, the phenomenon where mainly positive results are published and negative results are left on the shelf.”⁸

This phenomenon is strengthened by the way science is evaluated, namely on basis of the impact of a scientific publication - amongst other things, measured by the number of times that the publication is cited by others.

That may have been one of the reasons behind the decision of the KNAW, VSNU and NWO to scrap productivity in the shape of as many scientific publications as possible in the 2015-2021 Standard Evaluation Protocol (SEP), which describes the methods used to evaluate research at the Dutch Universities and NWO and KNAW institutes. The research groups are still evaluated in terms of their quality, social

relevance, viability and/or strategy.⁹ An extra factor such as social responsibility, and then particularly with respect to the use of laboratory animals and the strategy aimed at speeding up and strengthening the development and application of animal-free innovation, would have been a great addition and could probably still be included and otherwise in the next round from 2021.

In my opinion, the solution to the animal-related causes of the lack of reproducibility mainly lies in closer and more intensive cooperation between Laboratory Animal Science and the other scientific disciplines that work with animals in their research.

Besides the above reasons for the lack of reproducibility and validity in scientific procedures on animals, the lack of independence between the planning and implementation of the research is also a factor - that is, the lack of blinding and randomisation. Blinding means that the person who set up the trial doesn't know which laboratory animal was subjected to which treatment. Randomisation means that the treatment is randomly distributed over the laboratory animals in the experiment. The solution here could be to use the laboratory animal facility as an independent partner in the research. I'd like to discuss with the researchers how to implement the quality requirements for blinding and randomisation more efficiently by involving the Central Animal Facility more in the execution of the animal experiments.

Another equally important factor is the mutual cooperation between the Laboratory Animal Science centres, starting in the Netherlands with the Chair for “evidence based laboratory animal science” occupied by my colleague prof. Ritskes in Nijmegen and my colleagues in Utrecht, where I hope that the Chair vacated after the untimely death of professor Ohl, the successor to prof. Van Zutphen, will soon be filled.

Together, we can put Laboratory Animal Science Netherlands back on the map. The ongoing collaboration to create a new handbook for the laboratory animal science study programme would be a very good start. As would working together to strengthen the national and international position of

Laboratory Animal Science, each of us spurred on by our own interests and areas of expertise, to promote the welfare of the animals and the biomedical research.

The LUMC and Laboratory Animal Science

Fifteen years ago, I started working at the LUMC as head of the Central Animal Facility. At the time, we had a number of locations distributed over the Leiden Bioscience Park. The aim was to accommodate all the animal research in one central facility, based on the latest developments in terms of sound, high-quality laboratory animal management aimed at maximum protection of the animal and its welfare and health, as well as the conditions necessary to conduct high-quality research.

In the period from 2006 to 2007, the Central Animal Facility relocated in phases to our current premises and we increased the quality at the same time in terms of both managing the breeding of genetically modified mice and rats and the status of the colony's health, and also in terms of the range of specialist services. The laboratory animal pathology managed by dr. Salvatori has developed into an indispensable part of many research programmes at the LUMC and the UL. Such as Transgenesis Facility Leiden, TFL, run by prof. Verbeek and his team, which has been creating unique genetically modified mouse strains for the researchers of the LUMC and third parties for the past 17 years. Strains on which leading scientific publications are based.

Together with ErasmusMC in a Medical Delta context, we are now researching the best way to combine the transgenesis activities, and, in that way, provide an even better service to both institutes and other interested parties. The same applies to the other services we offer as the laboratory animal facilities of the ErasmusMC and the LUMC.

All of these things were and are only possible thanks to the support of the LUMC, and after 15 years I can conclude that everybody in the organisation - from the Executive Board right down to the work floor - feels passionate about taking proper

care of the animals. This is instrumental in creating a real culture of care. After all, you can only call it a culture of care after it has permeated deep into the heart of the organisation and is experienced and supported by everybody involved. But we do need to be vigilant and alert at all times if we want to maintain that care culture, raise it to a higher level and integrate it with the transition to animal-free innovation. After all, the continuous changeover of students, PhD students and postdocs is characteristic of academic institutes in which entire research groups come and go all the time.

Education

Education in Laboratory Animal Science plays a central role in creating and maintaining that "culture of care" and stimulating the right attitude towards the use of animals for scientific research.

I would like to emphasise here that what works well today can always be improved tomorrow.

The statutory Laboratory Animal Science course for researchers who intend to use animals in their research has a long tradition in the Netherlands and at the LUMC. The first nationwide Laboratory Animal Science course was developed in Utrecht. Utrecht was also home to the Laboratory Animal Welfare Officer post-graduate study programme until it was no longer necessary after the Experiments on Animals Act was revised. That doesn't alter the fact that the knowledge and skills of those former Laboratory Animal Welfare Officers, which is so essential to the work of the Animal Welfare Body, still needs to be transferred to future generations. So I look forward to talking to my colleagues in Utrecht about how that can be organised and done.

The Leiden tradition of the statutory three-week Laboratory Animal Science course was launched in 1993 by prof. Daha and Nibbering. Since 2002, I have had the privilege of organising the courses together with dr. Reuzel and since 2007 with drs. Meijers, supported by mrs. Imthorn. In the meantime, together with a large number of lecturers we have enlightened

an impressive number of students studying medicine, biology, biopharmacy and the biomedical sciences, as well as PhD students and postdocs, about the dilemmas they can face when conducting research with animals. We have told them what needs to be done to rightly accept responsibility for conducting research with animals. It is a course in attitude building - that is, learning the right attitude, the critical attitude, the right mind-set, the sensible mind-set - by giving people the instruments they need to make an informed choice - based on the 3Rs concept - Replacement, Reduction and Refinement.

In 2013, we were pleasantly surprised when the Federation of European Laboratory Animal Science Associations (FELASA^{VI}) accredited our course as the first Laboratory Animal Science course in the Netherlands. The Dutch Laboratory Animal Science study programme has a good reputation internationally. It's great to see that our fellow-coordinators from other Laboratory Animal Science courses now also want to have their courses accredited to consolidate our good reputation.

The good working relationship during the course coordinators' meeting, chaired by dr. Van der Valk, means that by discussing things and being open to each other's ideas and criticism we can keep the Laboratory Animal Science course up-to-date, and improve it where necessary. Till the introduction of the species specific modules, we often had animated discussions about the usefulness and necessity of using living animals. Here in Leiden we still do that, also for masterstudents, in the belief that it helps us achieve the aim of the course. This is often the first time that students pick up a living mouse or rat and stick a needle in it. It is precisely at times like these that students are confronted with emotions they never felt before. We believe it is better to experience these emotions at the start of a career, under controlled conditions and supervised by an instructor, rather than later, when career choices have already been made. It's their first contact with the animal, but it's not the targeted training that is needed to teach them to work independently. After the course, the students are authorised, but by no means competent.

Is it possible to permanently ingrain that attitude, that responsible mind-set in the students?

In my experience?

No!

But when there is a "culture of care", the chance of people not taking that responsibility seriously is less than when such a culture doesn't exist.

And I think the old Dutch proverb also applies here: "you're never too young to learn".

Here in Leiden, the Leiden University Graduate School of Teaching, ICLON for short, offers secondary school pupils the chance to give guest lessons. This is done in the context of their pre-university education affiliation programme. I'm currently preparing two of those lessons, which I hope secondary schools in Leiden and its environs will include in the curriculum for their new 2017-2018 school year. The aim is to familiarise secondary school pupils with every aspect of the animal experiment issue and encourage them to think about it so that they can form their own opinions.

Also in the education of a prospective doctor, biomedical scientist, biopharmacist and other professions where animals are used for research, it's never too early to focus on what sound scientific research with and without animals means.

In that framework, the "Scientific Conduct" study programme for Masters students in the biomedical and biopharmaceutical sciences was expanded for the first time this year with a lecture on research with animals. Last month was the first edition in which the lecture was included. It was a very positive experience. We also want to make the lecture part of the "Academic and Scientific Education" common thread in the study of Medicine.

Education in Laboratory Animal Science under the motto: "there's no time like the present to stimulate students to develop and embrace the right mind-set and a critical attitude to the usefulness and necessity of scientific procedures on animals".

Welfare research

This Chair also provides a platform for more research into different i.e. novel methods to understand and improve animal welfare and to provide the scientific evidence for refinement strategies for the animals still being used in animal experiments. This kind of research is essential if we aim to provide the animals with the best conditions and amenities so that their welfare is maximised under all conditions and so that reliable results can be achieved with those animals.

How can I otherwise take full responsibility for the “welfare” of the animals for which we’re responsible as the Central Animal Facility: are they there for the right reason, are they housed as comfortably as possible, and are they being properly looked after?

In the term “welfare”, besides the well-being of the individual laboratory animal, I also include the fact whether that laboratory animal could have been replaced. After all, it’s not for nothing that Laboratory Animal Science has the R of replacement as its first R. Despite this, most laboratory animal science research is motivated by the Rs of Reduction and Refinement.¹⁰

In 1997 Poole published an article in *Laboratory Animals* with the title: “Happy animals make good science.” In the article, he looks at whether it would be better not only for the animal if it was in good shape, but also for the quality of the scientific results that are achieved with that animal.¹¹

What is an “animal in good shape”?

In 1965, prof. Roger Brambell defined his five freedoms on the basis of a report compiled for the UK Government about farm animals.¹² According to the report, an animal’s well-being is ensured when all five freedoms are met. Therefore, these five freedoms are also fundamental to the discussion about the use of animals for scientific purposes. Since, I’m not always convinced that everybody knows them, regardless of the audience, I’d like to take this opportunity to name them:

1. freedom from hunger and thirst [*- by providing continuous access to fresh water and food*];
2. freedom from suffering [*- by providing the right type of living environment, including places to shelter and rest*];
3. freedom from pain, injury and sickness [*- through prevention and rapid diagnosis and treatment*];
4. the freedom to display normal behaviour [*- by providing enough suitable living space for the species and the presence of others of the same species*];
5. freedom from fear and distress [*- by providing living conditions for and treatment of the animals, aimed at preventing mental suffering*].

In research with animals, it is almost impossible not to violate one or more of these five freedoms at any time, because otherwise the aim of the animal experiment could not be achieved. But then the hardship or suffering for the individual animal must be kept to a minimum.

This is also very much part of the field of Laboratory Animal Science.

In the LUMC’s Central Animal Facility, we have fully digitised “Big Brother”-like cage systems for mice, which we use to monitor their activity and behaviour 24/7. For over two years, we have been part of a consortium of institutes that has tested and validated this new Digital Ventilated Cage (DVC™, Tecniplast SpA, Italy) technology and conducted welfare studies. What makes the system so unique is that it is the first housing system for mice in which all the requisite technology for researching the behaviour of the animal and analysing the condition of the immediate surroundings and the presence of food and water in and around the cage has been integrated under the normal housing conditions. In a rack with cages in an animal room and not in a separate experimental setting.

Together with the consortium partners, we’ve shown that this system can be used to detect deviant behaviour in animals sooner than the statutory daily inspections. But what’s even

more important is that we can detect behavioural displays that were not detected before - for example, because they can only be seen during the dark phase (*when the animals are active and we're asleep*). In other words:

- animal welfare problems are detected earlier and analysed in more detail,
- appropriate measures can be taken to resolve the problems, and
- more data is collected that can be used to analyse the results of the experiments for which the animals are being used and to draw the necessary conclusions and so they can contribute to the validity of the animal experiment.

A simple question such as: how does cage cleaning affect the animals? We know that it increases aggression and activity, but we have now also discovered that it can take a few days for normal behaviour to return. The question is then: What does that mean for the results of an ongoing experiment?

How is the lighting in the cage? The lighting in the animal rooms is mounted on the ceiling. That means that the animals in cages in the upper part of a rack receive more light than the animals in cages towards the bottom of the rack. The effects of this have not been empirically determined, but they do produce a bias or rather a confounder, an extra variable factor, namely light, that can affect the progress and therefore the results of experiments. In the DVC™ system, we can supply all the cages with their own light source and thus make sure that all the cages have the same light conditions; and then we can study whether the standardisation of light in the cages contributes to the reliability and quality of the experiment results.

And then of course there are ingrained practices in experiments. Just last month, an article was published that described the effect of picking up mice on the results of behavioural experiments.¹³ With the DVC™ system, we can measure the effects through time on the animal and on the group of animals in the same cage and potentially, therefore, on the results of experiments.

All this information about the animal and its behaviour is made available so that it can be taken into account when researchers are setting up and planning experiments and the results are being analysed. This way they contribute to the validity of the animal experiment. During their research, the researchers of the LUMC can use the DVC™ system to house their animals. Agreements have already been made in the context of the research programme on pain relief.

You are probably thinking that we should have known or could have guessed some of these things before now. Yes, a number of questions were researched up to a certain point in experimental behavioural configurations, but never in the actual housing situation in which the animals live on a daily basis. That is now finally possible with the DVC™ systems that became available over the past two years.

I'm fortunate to have been given the opportunity to study this in detail in the next few years and that I can talk about it here today.

Communication

And it is important to talk about this in the context of education and scientific conferences, and as important - if not more important - in stories for the wider public.

A number of you have never been in a laboratory animal centre. You are very welcome to come and visit our Central Animal Facility! You'll need to reserve about two hours for the visit. Because as well as the guided tour with background information, I would like to talk to you about what you have seen and what you think of it.

If you don't have time for a visit, I hope to be able to shortly present an updated website together with the Communication Directorate about our research with animals at the LUMC, where there is more information than in the past and where you can ask questions about scientific procedures on animals. After all, we've nothing to hide!

Social responsibility

Earlier, I mentioned the new version of the Standard Evaluation Protocol (SEP) from the KNAW, VSNU and NWO, in which the research groups are assessed solely in terms of their quality, social relevance, viability or strategy.⁹

In that context, an index that makes it clear how research institutes operate in the field of the three Rs would be a great addition to the data on laboratory animal use that must now be supplied by law to the Government every year. This type of index would enable those figures to be viewed in a wider context. The above advice from the NCad also mentions this type of 3R index.

Marja Zuidgeest of the Dutch Society for the Replacement of Animal Testing, Cyrille Krul of the Utrecht University of Applied Sciences and I have joined forces so that we can also create an index like this. The index is comparable to the Access-to-Medicine Index^{vii} that has been published every two years since 2008. This Access-to-Medicine Index ranks pharmaceutical companies in terms of the global availability of their medicines, but then particularly in the developing world. It is a relative and not an absolute index! The company that scores the highest in terms of the distribution and availability of its medicines - even in countries where this is difficult - is listed at the top of the rankings. In the last publication in late 2016, GlaxoSmithKline (GSK) topped the rankings for the third time in a row. GSK is working very hard to stay in that position. Other pharmaceutical companies are hot on its heels. The Access-to-Medicine Index has now such a high status that companies that are not on the list are having to explain themselves.

The Index is not a rigid measurement instrument, but is regularly refined to more accurately reflect reality. All the pharmaceutical companies now take the Index seriously and are trying to present itself in the best possible light. Again: relatively compared to the others.

In 2011, the SLIM project - short for Faster from Innovation to Users - was launched by the Ministry of Economic Affairs and

the provincial and local governments of Utrecht.^{viii} As part of the project, the foundations were laid and a draft proposal was developed for an international benchmark for implementing 3R methods by analogy with the Access-to-Medicine Index. At the end of the SLIM project, the conclusion was that a feasibility study must first be implemented. We - Cyrille Krul, also a participant in the SLIM project, Marja Zuidgeest and I - are going to do that in the LUMC and we hope the UMCU and the University of Utrecht will also take part. The aim is to use information that is already present at the institutes in the form of registrations and databases.

Why?

Because the projects that have been funded and labelled as research studies aimed at replacing scientific procedures on animals are obviously recognisable as contributions to 3R activities. But there are many other schemes and plans that are not being acknowledged or recognised in their own right. Such as investments being made by institutes in the context of technological and scientific progress with as a “by-product” the fact that they also contribute to the reduction and refinement of animal experiments, simply better science with fewer or even no animals.

We want to clearly show what institutes are doing to replace animals experiments, but also what they are doing to reduce and refine them and identify the related policy and give it a value - that's the aim of this 3R Index.

Replacement and the transition to animal free research methods

It's not for nothing that the R of Replacement is the first R.

I think it's no more than natural that this Academic Chair at the LUMC and the University of Leiden should open itself up as a platform on which it plans and implements those animal experiments on the basis of the research priority areas and facilitates and supervises them, and holds discussions about:

- which important research questions must be answered in the coming years

- and which technological developments must be deployed or expanded in this area.

This should be done to make the areas with the greatest opportunities for replacing animal experiments visible and accessible, but also to identify those areas where animal experiments will still be an indispensable part of the research practices.

The Chair and therefore the Central Animal Facility as a 3R platform.

This gives us the opportunity in the LUMC and the UL to be policy-rich and enterprising with the dossier of scientific procedures on animals, partly as an answer to political mobilisation: The Netherlands as an initiator of animal-free innovation and a trend-setter in the field by 2025.

I already made the comparison with the energy transition and the energy agreement^{1X} but that comparison doesn't apply to the funding. For the energy transition, 2 to 3 billion euros per year have been budgeted up to 2020. The government will fund a huge part of that amount by means of financing schemes, loans and guarantees. Up to now, the Ministry of Economic Affairs has not yet opened the public purse for the Agenda for Animal-free Innovation. But fingers crossed. There's still time for it to happen.

Future

The same applies to animal welfare research.

It is very difficult to find funding for this. Although the EU's research grant programmes, such as FP6 and 7, still included subsidies for animal welfare research, they all disappeared in the Horizon 2020 programme.

In the Netherlands, we have the ZonMW grant programme, also called: "More Knowledge with Fewer Animals", in which dr. Salvatori has now been successful twice with "laboratory animal replacement project proposals", but there is little or no funding available for animal welfare research.

Maybe we can do something with crowdfunding and maybe

I should actually start doing something about it here this afternoon... but I suppose that wouldn't be very hospitable of me so I won't bother you with it right now. However, it would be nice if a route called "transition to animal-free innovation" was added to the National Science Agenda, one in which financial space is reserved for refinement research to the benefit of the animals that will still be used in scientific procedures, and the quality of the science for which they are used.

After all, Laboratory Animal Science is enabler of maximising animal welfare and good science.

Acknowledgements

I would like to thank the Board of Directors of the LUMC and the Executive Board of the University of Leiden for establishing this new Academic Chair and particularly for the trust they place in me to do justice to this Chair.

I'd like to thank...

Thank you for your attention!

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Noten

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