Delivering Better Evidence with Non-Animal Studies

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Inaugural lecture 6 November 2019, Nijmegen, The Netherlands

Science and politics are working together

As a student of veterinary medicine, I wrote my Master's dissertation at the Laboratory Animal Science department, which is where I discovered my mission: to improve laboratory animal welfare and to improve animal research. My shining examples were Professor Bert van Zutphen, Professor Anton Beynen and Professor Vera Baumans. For my Master's dissertation, I studied over a hundred papers on atherosclerosis in rats. Though still a student, I was aware that the quality of many of the papers I read was substandard and that the results of such research, therefore, would be unable to make a fitting contribution to solving atherosclerosis in humans. I noticed that thousands of animals had been used without a purpose. This is what I meant to change.

Hence I spent the first twenty years of my academic career attempting to improve the quality of animal research. And though my career was doing very well when I attained a professorship in Odense, Denmark, in 1997, I barely managed to make any significant improvements in my field. While everyone endorsed my arguments, this, much to my astonishment, changed virtually nothing in actual fact. Until something occurred that helped me to make a U-turn: I read what Aristotle had said, and what he said was that if you want to change anything in the world, you are engaging in politics. Up until that point, as a scientist trying to change the world of laboratory animal science with sound arguments, I had been politics-averse. But if I wanted to change anything, I learned, I would have to engage in politics.

Much to my own surprise, then, I have achieved an awful lot more over the past ten years with my political approach than I did in the two decades before with the soundest of scientific arguments. Those first twenty years were not lost, of course, for the arguments I use to wield my political influence are built on a solid scientific foundation.

Invitation to Members of Parliament

When I was still head of the Central Animal Laboratory and Professor of Laboratory Animal Science, I took my first political step in 2011 by inviting all Members of Parliament that had animal testing in their portfolios. I invited them for a working visit to our animal facility in Nijmegen, and all responsible portfolio holders from all political parties accepted the

invitation: PvdA, GroenLinks, SP, D66, CDA and of course de Partij voor de Dieren (Animal Rights Party). The VVD (Liberals) were the only party that was not represented. These Members of Parliament were given an extended tour of the animal facility, and I told them what I was doing and what I was hoping to do. Many Parliamentarians had never visited an animal laboratory before, and they were most impressed with everything, including what had already been achieved to improve animal welfare.

During this visit, I told them about Systematic Reviews and the new course I had meant to take since 2008. Ever since my graduation, I had focused on implementing the 3Rs of Replacement, Reduction and Refinement. The then animal testing licence holder, Roelof de Wijkerslooth, who was also chairman of the Executive Board of Radboud University, felt that pursuing the 3Rs was so important that he awarded me a two-year starting grant in 2006 aiming to establish a service that would support researchers in attaining and implementing the 3Rs. Thanks to this grant, we were able to offer this service free of charge in 2006 and 2007, receiving 30 research requests each year.

As of 2008, we had to proceed without financial support, and this meant that researchers had to pay us for our research on alternatives. The research requests plummeted to zero! Though we had shown in those two years that we were able to make a significant contribution to research quality and to finding alternatives, requests stopped coming in 'because it cost money', irrespective of the substance of our arguments. Even the Animals Experimentations Act, which made implementation of available options for Replacement, Reduction and Refinement mandatory, was barely taken seriously as 'there was no funding available.'

This served as a trigger for us to examine the 3Rs scientifically as a paradox. This paradox entails that there is no money available to perform sound literature reviews to improve research quality and avoid the unnecessary repetition of studies, while there is a lot of money available for performing substandard new tests that, moreover, might possibly have been done before.

Research into the implementation of the 3Rs

We therefore decided to perform surveys and interviews to find out more about this paradox, first in student projects and then in a PhD research project, which were facilitated by grants from ZonMw and Radboud University's Reinier Post Foundation. Judith van Luijk successfully completed her PhD thesis on this subject in 2017 (Van Luijk 2017). The conclusion of our nationwide surveys amongst researchers and animal testing experts confirmed what we had observed in Nijmegen: everyone felt that the 3Rs were important but no one was prepared to spend either time or money on finding and applying them.

This rather sad conclusion was confirmed when we staged a national workshop involving representatives of researchers, animal welfare officers and animal experiment ethical review committees: everyone was aware that alternatives, if available, were neither found nor used, even though this was punishable by law. What we also discovered during this investigation was that there were more than 100 databases and websites with 3R information out there in the world, most of which were unknown to anyone, including to us.

Moreover, they were all different in their structure, content and search strategies, so even if your intentions as a researcher were good, you would soon fail to see the wood for the trees. Searching for the 3Rs, therefore, though legally required, scientifically useful and socially desirable, proved to be mission impossible in practice.

All this had to change, and I discovered how it could be done when I attended a lecture by clinical neurologist Malcolm MacLeod in Portugal in 2008. His lecture was about Systematic Review research, and I realised immediately that this was offering the solution I was looking for to address the challenges in our discipline. From that moment onwards, my team and I have dedicated ourselves to developing this methodology for preclinical research. Meanwhile this methodology has helped to improve the implementation of the 3Rs, to advance scientific quality and to make the value of animal tests transparent for human beings. This last goal in particular is of the essence. This is about translatability or translation.

Systematic Reviews

What are Systematic Reviews? This method arose in the clinical sciences in the 1980s and has been routinely performed for medical studies in humans since 1992. Systematic Reviews produce what is called evidence-based medicine. The organisation that coordinates Systematic Reviews for clinical research worldwide is the renowned Cochrane Collaboration. With the aid of this method, scientific evidence can be delivered to show that a particular therapy actually works. It is also considered to be the highest level of scientific evidence, as it produces an analysis of all publications that are already available in a manner that is as complete, objective and critical as possible, which is then summarised into a comprehensive survey of all available evidence.

The first step you take in a Systematic Review is the very precise formulation of the research question. Then you perform a search of all relevant studies, including those in Chinese and Japanese, in order to obtain a complete picture of all publications in a particular field. The data of all relevant articles are then identified, and the quality of the studies is assessed and interpreted: how well have these studies been performed and how reliable are their results? Subsequently, you extract all results from these articles and you perform a new statistical analysis of all articles together, the so-called meta-analysis. This then produces a survey of what all these articles, taken together, show.

As the multitude of articles that have been published often show conflicting results and conclusions, it is very special and very satisfactory from a scientific point of view that a Systematic Review often allows us to draw an unambiguous conclusion anyway on the basis of all previously published results. The quality and objectivity of this method are safeguarded because most steps in the process are performed by multiple people independently, after which the outcomes are compared. If there are any discrepancies, these are solved collectively if possible, but a third independent assessor is involved if necessary.

Together with my team, I gradually changed over from 3Rs research to Systematic Reviews of animal studies, and in 2012 we founded SYRCLE (www.syrcle.nl) during a first

international symposium here in Nijmegen. This is also where we organised the very first workshop for Systematic Reviews of animal studies. Clinical neurologist Malcolm MacLeod was the keynote speaker, and Sir Iain Chalmers, one of the founding members of the Cochrane Collaboration, delivered the closing remarks. He observed that the participants in our symposium outnumbered those attending the founding meeting of the Cochrane Collaboration. His presence was a huge honour for us as Sir Iain Chalmers is a very big name in medical science, but besides being a huge honour, it also served as an important political message in our strategy. Politics was represented by Esther Ouwehand from the Party of the Animals, who had a very clear video message of support for us. See **https://youtu.be/7ZS7bcy1g2M**.

SYRCLE stands for Systematic Review Center for Laboratory (animal) Experimentation. The word 'animal' has now been parenthesised because we are often asked to perform Systematic Reviews in the field of alternatives to animal testing. It was owing to crucial grants from the former Dean and current chairman of the Radboudumc Executive Committee, Paul Smits, and ZonMw that we have been able to develop and expand our work. As this method was new to the field of animal testing, there was a clearly felt need for education, and so, with the aid of ZonMw grants in particular, one-day workshops are now being given on various locations in the Netherlands. Workshop participants may also receive coaching afterwards if they are intending to undertake a Systematic Review themselves. To facilitate and improve search efforts, SYRCLE has produced search filters with search terms for animal tests in the two major international databases Pubmed and Embase in close collaboration with Alice Tillema of the Medical Library. These search filters make sure that all animal studies can be found as quickly and as comprehensively as possible.

To disseminate our education efforts, we have also established the international SYRCLE Ambassador Network, currently consisting of 30 ambassadors all over the world, from Australia to India and Brazil. They promote education and research in this methodology at local and national levels. SYRCLE gained important recognition when it was awarded the 2017 second Cochrane Reward prize for its work in the field of developing preclinical Systematic Reviews (https://www.cochrane.org/news/cochrane-reward-prize-2017-award-winner-syrcle). This prize aims to reward initiatives that endeavour to reduce wastage and enhance research value. The prize was launched in accordance to the journal *The Lancet* in 2014 in its so-called 'The Lancet REWARD campaign'. The Lancet REWARD campaign was also endorsed by Radboudumc as being a worthy goal (https://www.thelancet.com/campaigns/efficiency).

Advantages of Systematic Reviews

Because Systematic Reviews produce a survey of the literature that is as complete, critical and objective as possible, this makes scientific evidence transparent, which helps to avoid unnecessary duplication of animal tests. Let me give you an example. A Systematic Review performed at the Radboudumc surgery department by Simon Yauw (Yauw, 2015) showed that no fewer than 88 studies had been done to demonstrate that chemotherapy causes slower wound healing of the surgical joins after bowel tumour resection. The fact that chemotherapy has a negative effect on wound healing is now well known and does not require to be re-demonstrated after this Systematic Review was done. Without this

publication, dozens of studies on the same subject might still have been done, but thanks to this study, the likelihood of unnecessary replications has gone down considerably. As Systematic Reviews are generally easily found and well read, this publication prevents new animal studies from being done with this aim.

A Systematic Review may help to clarify what animal model or other model had best be used to answer a particular research question. In the case of cartilage problems in human joints, rat and mouse models are often used, but these do not prove to be good models at all for the human process because these defects always heal quickly in rodents whereas they do not do so in humans (De Vries 2012). This inventory by Rob de Vries showed that the use of veterinary patients such as horses might offer a possible alternative because the spontaneous cartilage problems in the joints of some horses are similar to those in humans. The study of new therapies in veterinary patients, the so-called 'one health' or 'one medicine' concept, is a promising line of research because it allows spontaneous disease processes to be studied in various animal species and humans, requiring fewer laboratory animals.

A disadvantage of Systematic Reviews

An unfortunate disadvantage of Systematic Reviews is that they show up not only the quality but also the lack of quality of animal experiments. This does not always please our fellow researchers. More than half of the thousands of articles that we have meanwhile analysed in Systematic Reviews show major gaps, even failing to mention the basic principles of good scientific research: randomisation and blinding. Or what is even worse: young researchers are often not even taught these basic principles. Randomisation and blinding are the basic principles of good scientific research because they serve to exclude our subjective influence on desired results as much as possible. In addition, we see that, even if we now have excellent (ARRIVE) guidelines for reporting animal experiments (Kilkenny 2010) that have been embraced by more than 1,000 scientific journals, these have not, or barely, led to the required improvements in reporting quality (Hair 2019).

Systematic Reviews and fundamental research

Amongst researchers doing fundamental research there is the prevailing idea that Systematic Reviews are unsuitable for their type of research. This is a major misconception. A Systematic Review collects all available information. It does not serve to constrain creativity and free thinking. On the contrary, it helps to make sure that someone with a bright idea can check whether someone else did not already have and research this bright idea. For fundamental research too it is of the utmost importance to prevent unnecessary repetition. Tristan Hollyer from Aarhus University performed a brilliant Systematic Review of fundamental neurological research, which led to several new insights which he published in the *Journal of Neurochemistry* (Hollyer 2019).

Systematic Reviews and alternatives

Systematic Reviews offer plenty of opportunity for identifying and developing alternatives to animal testing, such as Systematic Reviews of *in vitro* studies, on cell cultures, for instance

(Golbach 2016). In addition, Systematic Reviews have an enormous potential to validate alternatives or, in other words, to show that alternative testing methods may have reliable or perhaps even more reliable results for human beings. SYRCLE is currently focusing on using Systematic Reviews to discover, develop and validate alternatives to animal testing because the translation of animal testing results to human beings is an important theme.

Translation

There are several poignant examples of animal testing results that have led to major problems in the clinic and that might probably have been prevented if Systematic Reviews had been performed. As early as 2001, Janneke Horn already performed a systematic animal testing review because she noticed that the 'promising medicine' Nimodipine did not have the expected curative effects on cerebral ischaemia in humans. While several animal studies had shown positive results, and the clinical study had been based on these, her Systematic Review showed that all animal studies taken together did not show any positive effect (Horn 2001). There is every reason, therefore, to perform Systematic Reviews of animal studies to protect human beings. This is why animal tests are done, after all.

Another remarkable conclusion by Horn was that researchers did not wait for the results of animal studies to become available before launching human studies. Another example of incorrect conclusions from animal experiments causing problems in the clinic became clear from a study done by Pandora Pound. In a clinical study, the application of a new therapy appeared to be causing serious unforeseen side-effects: haemorrhages in the brain. These side-effects had not been observed in various studies in rats, but a Systematic Review showed that all animal studies together did actually reveal these side-effects (Pound 2004).

Medical ethical committees and preclinical Systematic Reviews

Let me give you some more examples. The Propatria trial is a clinical study in the Netherlands that was discontinued because of the high mortality rate in the group of treated patients. One of my senior scientific staff members in SYRCLE, Carlijn Hooijmans, performed a Systematic Review of the animal tests done for the Propatria study. Our study revealed that the therapy that had been applied in the animal tests did not match the treatment of patients in several respects (Hooijmans 2012). Animal studies and human studies, moreover, were also performed simultaneously in this case.

A final example. In January 2018, the *British Medical Journal* (BMJ), a leading journal, published a very thorough study on tuberculosis vaccination in children in South Africa (Cohen 2018). The clinical study showed no additional protective effects of this vaccination while such effects had been expected on the basis of animal studies. A Systematic Review of animal studies demonstrated, again, that the results of all animal studies together showed no positive effect. The clinical study on children in South Africa, therefore, need not have been performed. The detective-like investigation of the *British Medical Journal* also revealed that a study using the vaccine on monkeys had shown higher mortality rates but that the monkey study had been removed from applications to the medical ethical committee and to funding agencies for the clinical study. As these results were unwelcome, they were likely to diminish the study's chances of approval. The *British Medical Journal* calls this the 'pick and

mix approach', and unfortunately this pick and mix approach is in common usage. This, of course, is serious food for thought. The *British Medical Journal* gave us the honourable invitation to write an editorial on this matter, specifying what would be required to prevent it (Ritskes-Hoitinga and Wever 2018). In the meantime, our editorial has been published, and while I hope it will accomplish the necessary changes to benefit laboratory animals and patients, I frankly feel that we need to turn to politics for change to happen.

Parliamentary motions

Following the visit of members of Parliament to our laboratory in 2011 and in collaboration with the Partij voor de Dieren (Animal Rights Party), two motions were submitted to Parliament and accepted. Public opinion on the whole is highly critical on the matter of animal testing, and the Party for the Animals is the successful political representative of this critical voice. Under pressure of the electorate and the rise of the Party for the Animals, other political parties also began to champion this matter. The two Parliamentary motions, therefore, were adopted with a broad majority.

In the first motion, adopted in 2012, the government was requested to make Systematic Reviews mandatory for animal experiments, as had already been the case for clinical studies for a long time. The VVD (liberals) voted against, possibly because they had not attended the working visit and were therefore unfamiliar with a lot of background information. A second motion, submitted in 2014, accomplished that Systematic Reviews were made a compulsory subject in Laboratory Animal Science courses. Laboratory Animal Science courses are compulsory for anyone who will be performing animal experiments. With a grant from the Ministry of Economic Affairs, the ministry responsible at the time for enforcing the Animals Experimentations Act, we developed an e-learning module on preclinical Systematic Reviews, which could be made available free of charge. This e-learning module has now become a compulsory component of virtually all Laboratory Animal Science courses in the Netherlands.

I was surprised and delighted by the profound impact that politics appeared to have and started to realise that this was to be the way forward. The grants from ZonMw and the Ministry, awarded partly in consequence of these motions, are of crucial importance for further developments in this type of research, causing the Netherlands currently to be playing an exemplary role on the world stage. Within the given framework, ZonMw and the Ministry are doing truly pioneering work and, with other funders of animal testing being few and far between, truly help to improve the quality of animal testing and to further the implementation of the 3Rs.

Politics and goals and the transition to non-animal innovations

The two Parliamentary motions have been a great success and have really set us on our way. They have also given rise to insights that require us to significantly redefine our political goals for that is the only way to make any real progress. What should these goals be and how can we convince politics that they are worth pursuing?

When I was a member on the advisory committee supervising Meggie Pijnappel's PhD research with Professor Hub Zwart at Radboud University, I freely shared with her my political idea that we should be formulating concrete goals in the field of alternatives to animal testing. This may have influenced the main conclusion of her PhD thesis (Pijnappel 2016), which runs as follows: the Dutch policy on alternatives is straying, darting hither and thither, which prevents any progress from being made. The government should be setting the course in the matter and should also impel adjacent policy areas to move in this direction (https://www.ru.nl/fnwi/@1024941/proefdierreductie/; https://vroegevogels.bnnvara.nl/nieuws/proefdierbeleid-is-dolende). Even before she completed her PhD thesis, Meggie became the secretary of a think tank in our discipline, which allowed her to spread her ideas. The think tank then underlined the importance of non-animal innovations, mentioning Systematic Reviews as one of those non-animal innovations: https://issuu.com/meneerdeleeuw/docs/in-transitie-nederland-internationa.

When I consider the current influence of politics on our discipline, I am most impressed by how right Aristotle was. We set the ball rolling and the political gods appear to be smiling upon us. For what has happened? What happened was that the Netherlands, to the surprise of friend and foe alike, announced in 2016, through its undersecretary for Economic Affairs Martijn van Dam, that it had the ambition to be the world leader in the field of non-animal innovations by 2025.

And then the political gods had their way with it, for this is how this goal was interpreted internationally: 'The Netherlands to abandon all animal testing by 2025'. Wherever I go abroad, everyone is truly convinced that the Netherlands intends to abolish animal testing entirely by 2025. And even though this is internationally considered unattainable, it is nevertheless setting the new standard. Seeking to win favour with the political electorate, it has now become an international trend to formulate concrete goals in our discipline (https://www.scienceguide.nl/2018/12/wat-dierproeven-betreft-zijn-onderzoekers-oerconservatief/). The Dutch goal and its international rendition have major consequences. It was recently announced, for instance, that the Environmental Protection Agency in the United States will phase out animal testing for safety research purposes by 2035: https://www.epa.gov/newsreleases/administrator-wheeler-signs-memo-reduce-animal-testing-awards-425-million-advance.

So why do we actually do animal experiments?

When I wrote my Master's dissertation at the Laboratory Animal Science department in 1988 and concluded that the quality of published animal experiments was inadequate, I believed that the solution was to improve quality. But when I founded the 3R Research Centre in 2006, the pursuit of quality improvement appeared to be fruitless. As I was not the only scientist engaging with this matter, moreover, Sutherland (2012) arrived at yet another dramatic conclusion on very good grounds: even if the quality of laboratory animal research were to improve, this would not entail a demonstrably better predictive value for human beings. And if animal experiments have barely any predictive value and clinical trials do not await their results, the question that remains, then, is: why are all these animal experiments actually done?

To address the question why animal tests are actually done and how they ever got started, I launched a project in collaboration with Wim van Meurs, Professor of European Political History at Radboud University. In this project, Doortje Swaters, a history Master's student, performs historical research into the rise of mandatory animal testing. The first results make clear that most legislation follows in the wake of disasters. In the US, many people died in the 1930s after they had used antibiotics (Elixir Sulphanilamide), where it was not the medicine itself but the solvent that had been used that proved to be the culprit: https://www.the-scientist.com/foundations/the-elixir-tragedy-1937-39231. This led to the passing of the Food, Drug and Cosmetics Act in 1938, which gave the Food and Drug Administration the legal authority to monitor the safety of new medicines.

The Softenon drama in the 1960s also gave rise to new legislation involving animal testing, implying that medicines should henceforth be tested not only in pregnant rodents but also in a second animal species that was not directly related to rodents, such as dogs and pigs. The requirements that were made upon these animal tests did not appear to be founded on any scientific evidence, but they were rather serving as a disaster response mechanism, meant to show that something was being done. The reason why certain animal tests are mandatory, therefore, appears to be without scientific foundation, and their predictive value for human beings has not, or barely, been validated.

Animal testing alternatives are often better

So what are we actually doing when we do animal tests? This is a question to which Systematic Reviews provide a clear answer. A Systematic Review is a non-animal alternative because it produces new results and insights without performing new animal tests. In addition, a Systematic Review reveals the quality of published results and how well they can be translated to human beings. A Systematic Review, therefore, is the highest type of scientific evidence, and our provisional conclusion is that animal tests have no demonstrable predictive value for human beings and that alternative methods are available and have as much or even more predictive value.

At Radboudumc, for example, a highly successful alternative has been developed for so-called Extra Corporeal Membrane Oxygenation (ECMO) training, which is used to train hospital staff in dealing with premature babies in an intensive care unit. Previously, hospital teams were trained using lambs that were anaesthetised, but these days baby simulator dolls are used (https://vroegevogels.bnnvara.nl/nieuws/op-weg-naar-minder-proefdieren). These baby simulator dolls offer much better practical training opportunities than anaesthetised lambs because the dolls can be used indefinitely to simulate all sorts of situations.

Here's another example. By using computer databases with data on 10,000 known chemicals based on 800,000 animal studies, it is possible to predict how chemicals will behave. The computer model, an algorithm, can accurately predict the toxicity of tens of thousands of chemicals in nine types of toxicity tests (Luechtefeld, 2018). Algorithm-based prediction now outperforms new animal tests: while animal tests correctly predict toxicity in 70% of cases, the computer makes a correct toxicity prediction in 87% of cases. As new chemicals can also be compared with the chemicals contained in this database, the comparability of molecular

structures also allows a sound prediction to be made of certain toxic effects of these substances.

A third example. In 2017, the National Centre for the 3Rs in the UK awarded a prize for a computer simulation model https://www.altex.org/index.php/altex/announcement/view/57, in which human cardiac cells were exposed to 62 medicines and control substances. When these data were entered into a computer model, the model proved to be able to predict the medicine-induced risk of cardiac arrhythmia in human beings with 89% accuracy, while the accuracy of animal tests was 75% (Passini 2017).

The main conclusion for now is that animal testing alternatives are often and possibly always better than animal tests. The development of replacement alternatives to animal testing is stimulated by the working group on Transition to Non-Animal Innovations, in which I represent the Association of Universities in the Netherlands (VSNU) on the team. With regard to these new alternatives, it is essential that we do not follow the same path as that for animal tests. So in developing alternatives, these should be validated for their predictive value for human beings rather than be compared to existing and common animal tests. Unfortunately, this has been attempted too often, wrongly and in vain in the past.

Fewer laboratory animals by greater patient involvement

Most laboratory animal research is done for the benefit of patients. In the UK, the James Lind Alliance was founded aiming to allow patients, clinicians and funds to draft research programmes together (http://www.jla.nihr.ac.uk/), engaging in consultation to decide on research priorities in so-called Priority Setting Partnerships. This helped to make clear that patients with asthma, for example, did not want new medicines but improved training of their breathing technique, and this led to a clinical study in which asthma patients were offered breathing-related physiotherapy. The results were very positive: some asthma patients recovered fully while others had lower anxiety levels when they were having an asthma attack. This is a great example of patients being served without animals having to be sacrificed.

Europe

Let me reiterate that the phasing out of animal studies has meanwhile become an international trend and an EU focus. When the European Citizen's Initiative produced more than one million signatures against animal testing, a public debate was hosted in Brussels, causing the European Parliament to allocate more than €1 million to five pilot studies. The aim of these studies is to realise more and better education in the field of the 3Rs and particularly to achieve replacement of animal tests. SYRCLE is involved in two of these projects, which are conducted under the supervision of the EU's Joint Research Center and DG ENVironment in Brussels. I cannot help but add that this one million euros is in sharp contrast with the hundreds of millions of euros that continue to be spent on laboratory animal research every year and that it is high time for research funding to be reallocated in order to achieve better and validated alternatives without delay.

Global

Some more politics then. Once it had become clear to me that you need to have a top-down approach in addition to a bottom-up approach, it became imperative to know who the people are that have the power to change things. In addition to politicians, that would be the funders. By way of the Cochrane REWARD prize, I got in touch with a funders forum called Ensuring Value in Research, an international forum looking for ways to make sure that funds invested in research are actually well spent. The funders forum was founded by ZonMw in the Netherlands, the NIHR in the UK and PCORI in the United States. This funders forum has formulated ten guiding principles for research funding (https://sites.google.com/view/evir-funders-forum/guiding-principles).

I got in touch with them because they had focused on clinical studies exclusively up to that point and I felt that their guiding principles should also be applied to preclinical studies. The first joint steps to achieve this goal have meanwhile been taken, encouraged by the Netherlands, where several meetings have been held with various organisations such as ZonMw, the joint health funds SGF, the VSNU, the NFU and the KNAW. To my great delight the funders forum recently decided to establish a preclinical working group aiming to achieve the application of their guiding principles to preclinical research.

The goal: to abolish animal testing in 2035 at the very latest

Is there any point to animal testing? There certainly was in the past, if you bear in mind that the contraceptive pill would not have been developed without the aid of animal testing. In the meantime, however, we have alternatives that are increasingly and demonstrably doing a better job. I recently gave a lecture at a meeting of the European Society for Biomedical Research and Alcoholism in Lille, where the speaker before me quoted psychiatrist Stephen E. Hyman, who says the time has come to stop animal testing.

Hyman (2012) observed that great progress was made with medication for mental illnesses in the 1950s, but that this success caused its own downfall when certain animal tests, such as the forced swim test and the tail suspension test, were mistakenly adopted as the gold standard. These types of tests bear no similarity at all to human disease processes, causing previous success to evaporate. The upshot of all this is that the pharmaceutical industry has now virtually stopped developing medicines for mental illnesses while the need for them is high. Hyman claims that we live with paradigms, such as what he calls ‘misleading animal behavioral models’, that are perpetuated by science but that obstruct essential developments. He is, in my view, entirely right in arguing in favour of human models.

Let me finally touch upon a last aspect that often remains underexposed in debates on the usefulness of animal experiments. Because animals are often not a good model for humans, those substances that are active in humans often do not show a positive effect in animal tests, aspirin being a case in point: while this has all sorts of beneficial effects for humans, it offers no relief to any animal.

All in all, therefore, the usefulness of animal experiments, not only in public opinion but also in fact as demonstrated by Systematic Reviews, is highly dubious indeed. It would appear

that clinical science is already aware of this as a great many clinical studies are being launched without waiting for the results of animal tests to become available. It is high time, therefore, to announce that the old animal testing customs have outlived their usefulness.

Such an announcement would require courage, clear intermediate goals, long-term vision, the collaboration of many stakeholders and investments in the development of better alternatives. Dutch politicians are on the right track, and with my new chair I hope to encourage and support them to the best of my ability in their forward-looking policy. We are currently an international pioneer and, based on fact and reason, I believe we should continue to break new ground.

Considering all I have outlined above, therefore, I appeal to Dutch politics to embrace the goal of abolishing animal testing entirely by 2035 at the very latest. Following the international trend, President Trump has already decided that the Environmental Protection Agency will no longer be conducting animal experiments for safety research by 2035. On the basis of the facts, we can and we must aim for bigger goals. My appeal, therefore, is the following: let's make the Netherlands the first nation to be completely free of animal testing by 2035.

A word of thanks

When I consider who has played a crucial role in my work and my development, there is a long line of people that deserve a mention. I will name some of those, at the risk of overlooking others, for which I would like to offer my apologies in advance. My parents taught me that it is important to learn a lot because, as they said, 'that's always useful'. My eldest sister Minke has asked me twice in my life what I wanted to be. The first time I answered 'a vet'. The second time 'a professor'. I became both. This is also how I learned about the importance of setting goals and how important it is to put questions both to yourself and to others. Bert van Zutphen, Anton Beynen, Vera Baumans, Joop Koopman and Wim van der Gulden taught me my profession and fostered my love and understanding for the field of laboratory animal science.

Carel van Os did his utmost to realise a professorship for me at Radboudumc in 2005. I would like to thank Malcolm MacLeod because his lecture inspired me to engage in Systematic Reviews. Jeremy Grimshaw, the head of Cochrane Canada, invited me to take part in a conference of the Cochrane Collaboration, and we were then invited by Jeremy to sit on the Board of Directors of Evidence Synthesis International. Gert Jan van der Wilt and Paul Smits included our work in the research theme of the Nijmegen Center for Evidence Based Practice (NCEBP). Thanks to Bart Kiemeney we were also embedded in the new research theme of the Radboud Institute for Health Sciences (RIHS), and thanks to Wout Feitz in the theme of Regenerative Medicine. Many Systematic Reviews have been written in collaboration with the Surgery Department, and I owe a debt of gratitude to Harry van Goor, Michiel Warlé and Kees van Laarhoven. Maroeska Rovers, your support, your extensive knowledge and your enthusiasm to help us with your expertise on clinical studies have been hugely significant.

Where would we have been without the expert support of Alice Tillema of the Medical Library. For her statistical support, Joanna in ’t Hout is an invaluable resource. Rob Scholten, head of the Dutch Cochrane Center, we met in a debate on Systematic Reviews of animal tests held by the *Radbode*. When we met with quite a lot of opposition in those early days, you always encouraged us by saying that we were heading in the right direction and simply had to carry on.

SYRCLE colleagues Rob de Vries, Carlijn Hooijmans, Marlies Leenaars, Kim Wever, Judith van Luijk and Cathalijn Leenaars: without you, this topic would never have made it to where it is today. With our shared idealism, work ethic and sheer drive, we fuel each other because we are working to accomplish a better future for animals and human beings, which is what we pursue. I thank the Reinier Post Foundation, the Executive Committee and the Executive Board for their sustained support and funding, enabling us to continue our work. I thank Bart Kiemeney, Robert Opsteeg and Gert Jan van der Wilt for offering the possibility to include SYRCLE and my new chair in the Health Evidence Department since January 1, 2017. Despite our many evident successes, it has been a bumpy ride in financial respects and I truly value your support. I would like to thank Birgitte Kousholt and Gregers Wegener, my colleagues in Aarhus, for my appointment to the honorary Skou professorship and for their stimulating partnership.

A word of special thanks goes to Henk Smid, Barbara van der Linden and Erica van Oort at ZonMw, for their commitment to shaping our work and for collaborating in the funders forum. The developments that are taking place there are truly wonderful.

I would like to thank all my colleagues involved in the Transition to Non-Animal Innovations for so many stimulating meetings. It is most inspiring and very gratifying to see how so many things can change for the better so soon.

To my husband Rients, finally, I say: thank you.

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