The European Commission's Opinion Backing Use of Non-Human Primates in Research is Flawed

Scientific advisors to the commission have disregarded evidence of past failings and the achievements of new technologies, say *Margaret Clotworthy*, *Robert Coleman* and *Kathy Archibald*.

A recent opinion of the European Commission's Scientific Committee on Health and Environmental Risks (SCHER) that supports the use of non-human primates (NHPs) in biomedical research is scientifically flawed. It fails to evaluate in a critical manner the contributions to biomedical science that the committee assumes are made by NHP research and simply disregards proof of the contribution that human biology-based methods are now able to make.

The opinion, handed down in January, concluded that for many areas of biomedical research, there are, at present, no valid alternatives that would allow for a discontinuation in the use of NHPs[1,2]. SCHER's brief was to provide independent scientific information on the current status of possible replacements for NHPs. Yet the committee conspicuously fails to challenge its own assumption that NHP research is inherently efficacious – despite being presented with highly significant evidence to the contrary – and ignores the achievements of new technologies. The opinion also raises questions as to whether SCHER was suitably qualified to carry out the remit of the brief.

There are published several large-scale systematic reviews of NHP research that cast considerable doubt on the reliability and utility of NHPs for combating human diseases[3-7] – yet the opinion fails to reflect this.

SCHER concludes that the use of NHPs is essential in a number of important areas of research, including: safety testing of pharmaceuticals; the development of vaccines and therapies for infectious diseases such as HIV/AIDS; and the development, and testing, of treatments for neurological disorders such as Parkinson's disease.

However, no convincing case has been made for the value of NHPs in any of these areas of research. Moreover, there is powerful evidence of the unsuitability of NHP use in many cases.

On the drug safety testing front, 67% of NHP use is for testing pharmaceuticals[8]. Yet there are no published data that show that toxicity tests in NHPs are predictive of human outcomes. On the other hand, a paper published in 2008 concerning a much-quoted study of the predictivity of dogs and monkeys for the toxicity of anticancer drugs comments that [9]: "The data provide no statistically credible evidence that these animal models contribute any predictive value, either separately or in combination."

Some 34% of NHPs in regulatory safety tests undergo single dose toxicity tests. Yet such tests have been discredited by a large study, published in 2008, which was supported by the European Federation of Pharmaceutical Industries and Associations[10].

A stark example of how NHPs can fail to identify unacceptable adverse reactions in humans is provided by TeGenero's drug CD28-SuperMAB (TGN1412). The agent, which was being developed to treat B cell chronic lymphocytic leukaemia and rheumatoid arthritis, caused near-fatal side effects in its first human trial in 2006. A test using human cells has now been developed to detect the adverse effects that were missed by the animal tests[11].

In light of the lack of evidence to support using NHPs to test for pharmaceutical safety, state-of-the-art human-specific technologies (including microdosing, microdialysis and tests involving human tissues and DNA microarrays, as well as virtual patient technology) should be evaluated for their ability to predict human outcomes.

A direct comparison of the two approaches should be conducted, using a panel of drugs for which human and NHP data is already available. The Safety of Medicines (Evaluation) Bill currently before the UK parliament would require the UK government to commission such a comparison[12].

Until such a comparison has been conducted, it is not justifiable for SCHER to claim that there are insufficient alternative methods available to replace the use of NHPs in this area of research. Indeed, it appears likely that the replacement of NHPs by methods specific for humans should improve the protection of public health and safety as far as new medicines and vaccines are concerned.

In the area of HIV vaccine research, more than 80 vaccines for HIV have shown efficacy in NHPs but have gone on to fail in clinical trials[13]. As Anthony Fauci, director of the US National Institute of Allergy and Infectious Diseases, acknowledged[14]: "We've learnt that one of the animal models, the SHIV [monkey] model, really doesn't predict very well at all. At least we now know that you can get a situation where it looks like you are protecting against SHIV and you're not protecting at all in the human model – that's important."

Meanwhile, VaxDesign, a US company, has developed a model of the human immune system "to address inherent flaws with current animal testing models, namely that animals can never offer completely predictive results of a new vaccine or therapy because of basic physiological differences between humans and animals".

VaxDesign's president, chief executive and co-founder, William Warren, said[15]: "We know animal models do not translate to human responses... Animal models of treatments for HIV to psoriasis and flu are not representative of human responses." VaxDesign's approach is also supported by Wayne Koff, senior vice president of research and development at the International AIDS Vaccine Initiative. Dr Koff commented in the magazine *Time* last year[16]: "In the end, you can only extrapolate so much from a monkey model."

With regard to neurological research, SCHER states: "The application of deep-brain stimulation (DBS) in humans with Parkinson's disease derives from experiments in a NHP model." Yet this is incorrect: DBS was actually pioneered in humans[17]. Clinical research into such treatments preceded the NHP model of Parkinson's disease by decades[18]. Virtually all of our knowledge of Alzheimer's and Parkinson's has been gained by studying patients and their tissues: not primates.

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According to John Xuereb, director of the Cambridge Brain Bank Laboratory and the Wolfson Brain Imaging Centre (both based at the University of Cambridge in the UK)[19]: "Alzheimer's, Parkinson's and other neurodegenerative diseases occur in humans and it is in human tissue that we will find the answers to these diseases." Over 700 interventions have been published showing efficacy in animal stroke models. Of these, around 150 have been tested and been found to be ineffective in human stroke studies – sometimes harming patients[20]. Many scientists would agree with the statement by David Wiebers of the Mayo Clinic in the US that[21]: "Over-reliance upon such animal models may impede rather than advance scientific progress in the treatment of this disease."

Meanwhile, there has been a veritable explosion of imaging techniques, from magnetoencephalography and electroencephalography, through positron emission tomography and functional magnetic resonance imaging, to magnetic resonance spectroscopy, transcranial magnetic stimulation and diffusion tensor MRI. These techniques and many more have advanced our understanding of the human brain in health and disease far more than studies of NHPs. Ultimately, it is through study of the human brain that treatments for human neurological disorders will be found.

The SCHER opinion is exceptionally defensive of the use of NHPs. It says that "other species provide demonstrably unsatisfactory models in crucial respects", but it fails to recognise that NHPs often suffer the same limitations. The opinion is unjustifiably critical of microdosing and extraordinarily dismissive of the US National Academy of Sciences report on "Toxicity testing in the 21st century". This report, published in 2007, called for replacement of animal tests by "more efficient *in vitro* tests and computational techniques". However, SCHER concludes that this pertains only to chemicals and has no relevance for pharmaceuticals.

Was SCHER the wrong body?

We believe that SCHER was the wrong body to be entrusted with this important brief. Its mandate covers non-medical health and environmental safety issues. In our opinion, its members have insufficient relevant expertise and their independence is compromised, since many of them are current or former animal researchers. The commission says that some of SCHER's members have a relevant background in pharmacology and that experts involved in drafting the opinion work both with animals and with other methods such as human epidemiology, *in vitro* and computational methods. It also says that SCHER is the most appropriate framework for providing advice on alternatives to animal testing and that its working group included several external experts with a suitable profile covering all the relevant areas of expertise.

However, since the purpose of the opinion was to assess the ability of new technologies to replace NHPs in specific research areas, the working group should have had expertise in those new technologies. Given the wholly inadequate treatment of the current status of technologies that we believe are indisputably superior to the use of NHPs in many cases, we maintain that insufficient expertise in those areas was available.

At a hearing hosted by SCHER on 6 November 2008, senior representatives of both the UK government and a major industrial user of NHPs warned that the opinion would not be taken seriously if it were as one-sided as the draft opinion had been. Furthermore, suitably qualified scientists nominated by groups opposing the use of NHPs were refused permission to attend the meeting. The Safer Medicines Campaign was not even invited, contrary to claims that all contributors to the consultation were invited to participate.

In the absence of evidence to the contrary, we question SCHER's opinion that the use of NHPs is essential for testing pharmaceutical products, including vaccines and neuroprotective agents, for either safety or efficacy. We believe that the effectiveness of tests in NHPs should be measured against the latest human-specific technologies before pronouncements can be made concerning which types of tests are indispensable.

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