

Letters

Animal and Human Pain

Animal Pain Research is Scientifically Valid: Whether it is Morally Acceptable is a Separate Question

Dear Editor,

A recent article by Langley and colleagues argued that animal pain research has failed scientifically and is morally unacceptable.¹ The first argument was too strongly stated, and the second was not adequately separated from the first.

It is true that not all animal models result in success. Langley *et al.* cited the lack of efficacy of NK1 receptor antagonists in clinical trials as emblematic of the problem. The failure of the NK1 compounds to translate from animal to human is disappointing, but one failure should not cast doubt on the utility of all animal models. The development of the analgesic, ziconotide (Prialt™), is a clear counter example of “rational drug design” starting from basic science in animals. This one success does not secure the utility of animal models for every application but, overall, reviews indicate that animal models predict the analgesic efficacy of clinically effective compounds.^{2,3}

Langley *et al.* also argue that animal models can never adequately capture the complex psychological nature of pain. There is obviously considerable truth in this statement, but animal models are developing, and newer approaches incorporate operant techniques,⁴ while others include some cognitive and emotional changes that attend chronic pain.⁵ Suggesting that functional neuroimaging, genotyping, tissue databanks and epidemiology, provide a better way to capture the psychological nature of pain, overstates what those technologies can deliver. Animal models cannot deliver the entire complexity of the psychological experience, but nor can colourful brain images, DNA, tissue fragments or population statistics.

Undoubtedly, pain is a proper subject matter for psychologists and clinical researchers, but it will become fully comprehensible only when subjected to investigation by basic scientists as well. All the various approaches to understanding pain have advantages and limitations, and the binary division of the field into good and bad approaches falsely characterises the problem. Combining different approaches drives understanding and drug development.

Animal pain research is technically and scientifically valid, but that does not mean that animal research is morally appropriate. The moral case against animal research is well stated elsewhere.⁶ In summary, the argument is that animals are “subjects of a life”, so what happens to them matters to them. In this view, animal experimentation is immoral, because, just like us, animals have an inalienable right to live the lives that matter to them. We do not agree with this characterisation of animal life, but, critically, we cannot cut through this argument by proffering good, scientifically valid, experiments that yield useful therapies. The scientific validity of animal research does not resolve the ethical desirability of animal research. Cutting the sciatic nerve in an animal does not advance the welfare interests of the animal, and cannot be solely justified by advances toward understanding neuropathic pain. We do not cut the sciatic nerve in human beings to understand neuropathic pain, because such experimentation would be immoral. We believe that animals are sufficiently different from us that pursuing experimentation with animals to advance human interests is morally justified. Differences of opinion on this point stem from different views of what it is to be human — not from different views of what it is to be scientific.

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Better Models of Human Pain

Dear Editor,

In August, the online publication, *Spiked*, carried a piece entitled *Humans are more important than animals*,¹ written by Stuart Derbyshire from the University of Birmingham.

The article attacked our report of an expert workshop organised by *Focus on Alternatives*,² on the opportunities and challenges of using ethically conducted volunteer studies to replace animals in human pain research. Our report³ appeared in *NeuroImage*, a peer-reviewed specialist journal. Derbyshire claimed that I (as lead author), or *Focus on Alternatives*, somehow “tricked” leading pain researchers into putting their names to a paper which unfairly represented the workshop they attended, and that the report was published without their full agreement. In addition, he asserted that the ethics of using animals have no place in a scientific paper.

All these assertions are wrong. Each expert participant knew and agreed with the workshop approach: to review the potential of human studies to replace animals in pain research and in developing better therapies. We asked our experts to start from the assumption that human-based approaches, where ethical and scientifically feasible, are preferable to animal experiments. This remit was clearly stated in our report, and is in the spirit both of British⁴ and European legislation on animal experiments. In pain research, human neuroimaging offers more-relevant and more-reliable data, overcoming many of the shortcomings of animal research.

Derbyshire’s suggestion that “Chris Langley... is probably responsible for the tone of the paper being negative about the prospects for animal research” in this field, is way off the mark. Our participants openly discussed the limitations of animal models, well known to pain researchers, and the report reflects that consensus view. One of *NeuroImage*’s reviewers told us it was insufficiently critical of animal use in pain research. In his *Spiked* article, Derbyshire himself admitted that “we are suffering from some overblown expectations of what animal models can deliver...”.

Derbyshire claimed that *Focus on Alternatives* somehow “played a trick” by writing a report which “layered an ethical objection” on top of a scientific case — and hence brought about a “propaganda coup”. All our authors saw, actively contributed to and approved our report, in the draft and submitted versions. Derbyshire’s statement shows a lack of understanding of the nature of science: it is a human activity embedded in a complex ethical, cultural and practical matrix. As we pointed out in our paper: “These scientific and ethical concerns about animal-based research, including in the area of pain research, are reflected both in British and European legislation, which requires the replacement, reduction and refinement of animal experiments wherever feasible”.

Derbyshire further opined that this “trick” had not led previously to publications in specialist journals. However, my colleagues and I have indeed published other scientific articles in specialist journals on replacing animal experiments, all of which discuss ethical issues.^{5–8}

Stuart Derbyshire should accept that both scientific and ethical concerns about animal experiments are valid, and, in the form of the cost/benefit assessment required before animal use is licensed, have been at the heart of British legislation⁴ for more than 20 years. His unfounded accusations are not helpful when considering how the legislation might be fully implemented in the 21st century.

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¹ Derbyshire, S. (2008). Humans are more important than animals. *Spiked Science*, 26.08.08. Website <http://www.spiked-online.com/index.php?site/article/5647/>

² *Focus on Alternatives* brings together British non-governmental organisations funding the development or promoting the acceptance of research methods that replace laboratory animals.

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Estimates of Worldwide Laboratory Animal Use

127 Million Non-human Vertebrates Used Worldwide for Scientific Purposes in 2005

Dear Editor,

Taylor and colleagues are to be commended for their exceedingly informative estimates of national and worldwide laboratory animal use in 2005.¹ Reasonably accurate assessments of animal use, both in specific countries, and globally, over time, are fundamental when assessing compliance with Three Rs strategies of Replacement, Refinement and Reduction of animal use,² or when seeking to identify regions in which implementation is relatively advanced or particularly poor.

After adjusting official data for 37 countries to match EU definitions of animals and experimental procedures, and other relevant EU criteria,³ Taylor and colleagues estimated that a total of 50,425,021 animals were used in 2005. By demonstrating a highly significant, positive linear correlation between animal use in these countries and animal study publication rates the following year, they were able to predict that 7,914,951 additional animals were used in 142 remaining countries for which only publication figures were available. They included all nations with a human population greater than 200,000. In total, they estimated that 58,339,972 living non-human vertebrates were subjected to fundamental or medically-applied biomedical research, toxicity testing, or educational use, within these 179 countries, in 2005.

Additional animal use

Although not included within these EU definitions, animals killed for the provision of experimental tissues, animals used to maintain established genetically-modified (GM) strains, or bred for laboratory use but killed as surplus to requirements, also give rise to serious bioethical concerns, and are important when considering the merits of laboratory animal use. When these additional categories were included, the estimate increased by 97.6%, to a total of 115,279,785 non-human vertebrates used worldwide.

Substantial though these estimates are, they nevertheless appear to have been overly conservative, because they relied on 'arithmetic,' or unweighted, rather than 'weighted', means. Consider, for exam-

ple, the case of animals used to maintain GM strains. As reported by Taylor and colleagues, data was available for only two countries:

- In Great Britain (GB), data were available for 2005. 1,874,207 animals were used for experimental purposes as defined within the EU (GB_{EU}), and an additional 630,755 procedures were conducted to maintain GM strains (GB_{GM} ; in this case, the number of procedures was likely to equal the number of animals used). $GB_{TOT} = GB_{EU} + GB_{GM} = 2,504,962$, and $GB_{TOT}/GB_{EU} = 1.337$. Hence, an extra 33.7% of animals were used to maintain GM strains.
- In The Netherlands (NL), NL_{GM} was unknown for 2005, but was 3,834 in 2006. So, for 2005, Taylor and colleagues assumed an identical NL_{GM} of 3,834, which they used in conjunction with the 2006 NL_{EU} of 523,956, to maintain the 2006 proportion. $NL_{TOT} = NL_{EU} + NL_{GM} = 527,790$, and $NL_{TOT}/NL_{EU} = 1.007$. So, an extra 0.7% of animals were used to maintain GM strains.

By according an equal weighting of 0.5 to both the GB and NL proportions of 1.337 and 1.007, respectively, Taylor and colleagues derived an arithmetic mean of 1.172, representing an additional 17.2% of animals used to maintain GM strains in 2005. However, the contributions of GB and NL were not equal, because $GB_{TOT} = 2,504,962$ is quantitatively far more significant than $NL_{TOT} = 527,790$.

Weighted means accord an importance or 'weight' to each contributing element that accurately reflects its proportional contribution to the whole. The derivation of weighted means is described at the statistical website <http://www.statistics.com/resources/glossary/w/wmean.php>, and elsewhere. In this case, the contribution of GB should be accorded greater weighting than that of NL. The correct weighting factor for GB is $GB_{TOT}/(GB_{TOT} + NL_{TOT}) = 0.826$, and the correct weighting factor for NL is $NL_{TOT}/(GB_{TOT} + NL_{TOT}) = 0.174$.

Hence, whereas the arithmetic mean = $[0.5 \times GB_{TOT}/GB_{EU}] + [0.5 \times NL_{TOT}/NL_{EU}]$, the weighted mean = $[\{GB_{TOT}/(GB_{TOT} + NL_{TOT})\} \times GB_{TOT}/GB_{EU}] + [\{NL_{TOT}/(GB_{TOT} + NL_{TOT})\} \times NL_{TOT}/NL_{EU}] = [0.826 \times 1.337] + [0.174 \times 1.007] = 1.280$, or, without introducing rounding approximations into the formula, 1.279. This represents an increase of 27.9%, rather than 17.2%, when animals used to maintain GM strains are considered.

Similarly, weighted means can be derived to estimate the number of animals killed for the provision of experimental tissues (21.6%), and bred for laboratory use but killed as surplus to requirements (68.1%) (Table 1).

Table 1: Proportional increases in laboratory animal use

| Animal Use | Arithmetic Mean | Weighted Mean |
|---------------------------|-----------------|---------------|
| Provision of tissues | 21.1 | 21.6 |
| Maintenance of GM strains | 17.2 | 27.9 |
| Surplus to requirements | 59.3 | 68.1 |
| Total | 97.6 | 117.6 |

Worldwide animal use in 2005

Hence, in addition to the 58,339,972 living non-human vertebrates predicted by Taylor and colleagues, approximately 68,607,807 animals (117.6%) may have been killed for the provision of experimental tissues, used to maintain established GM strains, or bred for laboratory use but killed as surplus to requirements. This results in a grand total of almost 127 million non-human vertebrates used worldwide in 2005.

Estimate limitations

As stated by Taylor and colleagues, however, the very limited number of countries for which data were available markedly limits the reliability of these additional estimates. Numbers of animals killed for the provision of experimental tissues were available for six countries, while numbers of animals used to maintain GM strains, or bred for laboratory use but killed as surplus to requirements, were available for only two countries, in each case. On the other hand, the EU countries involved often used very large numbers of animals, somewhat increasing the reliability of the estimations derived.

Furthermore, in each of these three cases, the proportions of animals used in 2005 were not directly available for some countries, and so were assumed to be identical to those derived by using figures from the closest available years. For those instances for which data were available, the errors introduced by such assumptions appeared to be small. For example, when compared to the 2005 NL_{EU} of 531,199, the 2006 NL_{EU} of 523,956 was only 1.4% lower. Nevertheless, as acknowledged by Taylor and colleagues, these estimates include a number of significant approximations. Despite these, they are considerably more reliable than previous estimates, which have largely been based on varying expert opinions, or very limited surveys.

Despite their magnitude, it appears likely that these estimates remain highly conservative. As identified by Taylor and colleagues, for example,

their estimate of 17.3 million living vertebrates used within the USA is very significantly less than a 2000 US Animal Plant Health Inspection Service estimate of 31–156 million, based on extrapolation from the results of a survey of only 50 of 2,000 research institutions.⁴ Furthermore, these estimates exclude several other categories of concern, such as some invertebrate species now understood to have advanced capacity for suffering, including certain cephalopods, and studies on advanced fetal developmental stages.

Conclusions

Despite the conservatism of these estimates, and the exclusion of some categories of concern, the total approximation of 127 million laboratory animals used worldwide in 2005 remains enormous, by any reasonable standard. It clearly demonstrates the need for considerably greater compliance with the Three Rs — which are universally recognised as an essential component of good laboratory animal practice, both for ethical reasons, and to increase the quality of the research and the robustness of subsequent results.

To increase the reliability and international comparability of laboratory animal estimates, thereby facilitating governmental and public scrutiny of the utility of social expenditure on associated research, considerably greater reporting and harmonisation of laboratory animal statistics internationally is also required. The overwhelming majority of countries that currently fail to provide adequate official statistics, should begin to do so, in a coordinated fashion.

Where laboratory animal use is large overall, or disproportionately large in comparison to countries with similar research budgets or publication rates, or is increasing over time, mechanisms to increase compliance with the Three Rs are likely to be particularly necessary.

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Estimates for Worldwide Laboratory Animal Use in 2005: Authors' Response

Dear Editor,

We thank Andrew Knight for his comments on our paper.¹ He suggests the use of weighted means as an alternative way of calculating the animal-use figure that includes extrapolations for animals killed only for tissue supply, to maintain genetically-modified strains and animals bred for laboratory use but considered as surplus to requirements. Neither we nor our reviewers suggested the use of weighted means and, whilst it might be an appropriate approach, it adds little to the reliability of our extrapolations. Consultation with a senior, independent statistician has confirmed this position.

The final extrapolations leading to our “more-comprehensive” global total of 115.3 million were based on the average percentage of animals reported by only five countries for animals killed only for tissue supply; by two countries for animals used to maintain breeding colonies; and by two countries for animals bred for laboratory use but considered as surplus to requirements.¹ Given this less than ideal sample size, any mean (no matter how calculated) does not command complete confidence, a caveat given in our original paper.

We could have presented our headline figure of 115.3 million animals within a range, placing the

mean in its correct context. The range could be derived by adding the final figure derived from the model (58,339,972) to the sum of the smallest percentage for each of the three additional animal uses and the sum of the largest percentage for each of the three additional animal uses (see Table 1). This results in a final range figure of 82,434,380 to 154,075,866 animals used in 2005 worldwide (82 to 154 million). This range would encompass Andrew’s weighted mean estimate and the possibility that animal use by countries such as USA and China has been underestimated by our approach — a possibility strongly suspected by estimates provided by both those working with laboratory animals² and surveying their use.³

We reiterate our assertion that what is now needed is more complete and accurate statistics from more countries, especially those who use animals heavily. Our estimates for global animal use remain the best to date, although we acknowledge they are frustratingly incomplete.

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Table 1: Calculating the range for the final extrapolated figure for animal use

| Additional animal use | Smallest percentage | Largest percentage |
|-----------------------------------------------------------------------|------------------------------|---------------------------|
| Provision of tissues | 2.4% (Norway, 2005) | 50.1% (Sweden, 2005) |
| Maintenance of GM strains | 0.7% (The Netherlands, 2006) | 33.7% (Britain, 2005) |
| Surplus to requirements | 38.2% (Norway, 2005) | 80.3% (Britain, 2005) |
| Total percentage (extrapolation factor) | 41.3% (1.413) | 164.1% (2.641) |
| Final estimate (total of 58,339,972 plus extrapolation factor) | 82,434,380 | 154,075,866 |

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