

these studies used a reasonable number of animals. We must realize, however, that this is only an inference on our part. Therefore, some rationale beyond a simple literature citation would provide more credence to the selected number of animals.

Finally, we consider a protocol that merely states the number of animals needed to produce enough of a certain protein or other substance. We submit that this does provide a rationale but is quite weak in and of itself. Such a rationale can be strengthened substantially by ensuring that the protocol also states, for example, the total quantity of the protein needed and the amount that can be typically be collected from an individual animal. Using this information, one can reasonably deduce the rationale for the selected number of animals.

1. Russell, W.M.S. & Burch, R.L. *The Principles of Humane Experimental Technique* (Methuen and Company, London, 1959).
2. Institute for Laboratory Animal Research, National Research Council. *Guide for the Care and Use of Laboratory Animals* (National Academy Press, Washington, DC, 1996).

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RESPONSE

Precise justification is needed

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Covelli must be commended for his conscientiousness regarding the number of animals necessary in a protocol and for setting up an IACUC subcommittee to review the available literature on animal number justification.

The number of animals that is appropriate for a specific protocol depends on complicated variables, including the type of study proposed. Thus, federal policies and regulations on animal number justification are deliberately ambiguous, to allow enough flexibility to cover various study types and models in animal use protocols. For instance, justification for teaching protocols will differ from that of breeding studies. Likewise, statistical justification is appropriate for

certain studies but not others. Typically, pilot studies to formulate hypotheses or comparative studies to determine whether two or more values are equivalent will require statistical animal number justification, whereas teaching or breeding protocols will not, but the number of animals used must be justified regardless.

Covelli's subcommittee rightly concluded that the most definitive statement about animal number justification is that offered by the *Guide*¹, which is incorporated into the PHS Policy², indicating a 'need to justify the number of animals required and to use statistical methods whenever possible'. However, the subcommittee should have cautioned that the number of animals used should be minimized and that, no matter the type of study, a rationale for the number of animals used must be provided. In my opinion, Covelli was not right in claiming that the IACUC can accept 'fairly loose' criteria for justifying the number of animals to be used. I feel that justification of animal numbers used in a study must address alternatives and the 3Rs (replacement, refinement and reduction)³ as well as the type of study. The justification for the number of animals needed should not be based on how many experiments laboratory personnel can perform per week, month or year; neither can the cost of animals used be the determinant for preferring a particular species or model over another. Rather, the species and models that are most appropriate for the study should be used.

Accepting 'fairly loose' criteria for justifying the number of animals used in a study could be interpreted by researchers to mean any statement would be acceptable, without careful thought as to whether the number of animals to be used is justified. Such an interpretation would defeat Covelli's desire for a reasonable assurance that the smallest number of animals required for scientifically valid results were used. Statements such as 'in our experience, this is the minimum number of animals needed for statistical significance' do not provide enough justification. Suppose the animal numbers used 'from experience' were large owing to a lack of procedural refinement on the part of the investigator(s). In accepting this rationale, the IACUC would not be ensuring that the proper justification had been provided.

1. Institute for Laboratory Animal Research, National Research Council. *Guide for the Care and Use of Laboratory Animals* (National Academy Press, Washington, DC, 1996).
2. Public Health Service. *Policy on Humane Care and Use of Laboratory Animals* (US Department of Health and Human Services, Washington, DC, 1986; reprinted 2002).
3. Russell, W.M.S. & Burch, R.L. *The Principles of Humane Experimental Technique* (Methuen and Company, London, 1959).

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RESPONSE

Statistics should be used

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The IACUC subcommittee has done a thorough review of regulatory guidance concerning animal number justification. Unfortunately, there is little specific advice available outside of US Government Principles¹ (Principle 3: 'the animals selected for a procedure should be... the minimum number required to obtain valid results') and the *Guide*² ('whenever possible, the number of animals requested should be justified statistically'). As with many performance standards, the level of detail required in the justification is left to local IACUCs' judgment.

Good justifications can be made without statistics, depending on the type of protocol submitted for review. For example, training protocols often justify the number of animals by stating the number of people needing to be trained in a certain procedure and the number of animals needed to adequately train each person. Although there are no statistics appropriate to this circumstance, the IACUC still needs to evaluate the justification to ensure that the minimum number of animals will be used. The IACUC should consider whether all the people listed really need to be trained in the procedure or whether training a subset of that group would be enough. The IACUC should evaluate whether that many animals are really needed to train each person. Could the use of videos, computer simulations or inanimate models such as the Koken rat