Jerald Silverman, DVM, Column Coordinator

Cost:benefit evaluations for research protocols

Dr. Mattie Rosinski researched the effects of cigarette smoking on health. Over the years, she and her colleagues had studied various nitrosamines, nicotine, smoking cessation aids and other substances, primarily using mice as animal models. Rosinski's most recent IACUC application proposed to use nearly 200 mice to investigate cellular stress in response to tobacco smoke exposure. The protocol clearly described the rationale for the study, the need for live animals, a statistical justification for the numbers of mice in each study group and so forth. The protocol also stated that it was critically necessary to wait until the animals started to exhibit moderately severe clinical signs of distress from broncho-alveolar irritation from tobacco smoke exposure before euthanizing them. The protocol described in some detail the clinical signs to be monitored and the reasons why an earlier study endpoint could not be used.

In past years, none of Rosinski's IACUC protocols had been seriously questioned, but Brittany Paulson, a new graduate student on the IACUC, reviewed Rosinski's protocol in a different manner than had been done in the past. At the full committee meeting, Paulson said she clearly understood Rosinski's rationale for choosing the study endpoint described in the protocol and the reasons why an earlier one could not be used. But Paulson questioned the benefit of the study compared with the distress that the animals would undergo. "It's not that I think there is no value at all to this study," said Paulson, "but study after study has demonstrated the harmful effects of tobacco and the results of this study may just put another nail in the coffin. In England, where I come from, we would have to weigh the cost of suffering to the animals against the benefit to society that might arise from this study. I see no such analysis here."

Larry Covelli, the IACUC chairman, quickly responded that the US system differs from the English system. He noted that Rosinski's study was funded by the National Institutes of Health, but before the funding was approved, a review board of experts in the field had agreed on the importance of the question Rosinski was asking, the quality of her proposed methods and her ability to carry out the study. "I understand all of that," said Paulson, "but that's not what I'm talking about. The study may have some importance, but is it important enough to justify the use of animals and their anticipated degree of pain or distress? Who looks at that question?"

Do you believe that the cost:benefit ratio of a proposed study, as expressed by Paulson, is evaluated before research with animals begins? If not, is such an evaluation needed? Should it be part of the IACUC review process, or should it be considered elsewhere?

RESPONSE

Pure ethical review

Robert Quinn, DVM, Dipl. ACLAM

Neither the Public Health Service (PHS) *Policy on Humane Care and Use of Laboratory Animals*¹, the Animal Welfare Act regulations² nor the *Guide for the Care and Use of Laboratory Animals*³ requires the IACUC to carry out this type of review. The impetus for such review is very similar in scope to the motivation for IACUCs to carry out scientific review of protocols. In reference to scientific review, the PHS *Policy*¹ states, "[s]uch guidelines shall not be construed to prescribe methods of research." Even in light of this statement, the IACUC is required to review the rationale for involving animals, the appropriateness of the species and numbers of animals to

be used and the minimization of pain and distress in the conduct of 'scientifically valuable research'¹. This, of course, implies that the IACUC must be assured that the science is valuable; otherwise, there is no reasonable way to evaluate these factors.

These same requirements may be interpreted to imply that ethical review is required, though not as clearly as scientific review. When considering animal research, most people think of biomedical research, which is most often done in pursuit of understanding disease or finding cures that, hopefully, will lead to health benefits for humans or animals. With biomedical research, it is fairly simple to understand the potential benefits to society. If there were no potential health benefits from biomedical research, it would be extremely difficult to justify the necessity of a study at all, let alone the necessity to use animals.

Unfortunately, science at its most basic is just the pursuit of knowledge. Research may be scientifically valuable even in the absence of a clear idea of how it may benefit health or well-being in the future. In a sense, if research tells us something we don't already know, then it is scientifically valuable. The pursuit of knowledge is a step-wise progression, and often beneficial results occur only after a critical mass of seemingly unrelated knowledge is linked together. If the initial studies that lacked a clear indication of benefit were not done, then this critical mass of knowledge would never develop and these benefits would never be discovered.

In addition to the difficulty of judging the benefits of basic research, the IACUC must also contend with the 'ethical mathematics' of this type of evaluation. How do you equate the suffering of one species to the benefits of another? This question has been