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SPECIAL TOPIC OVERVIEW

*Special Topic Overview*

# Pain Management Standards in the Eighth Edition of the *Guide for the Care and Use of Laboratory Animals*

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**The eighth edition *Guide for the Care and Use of Laboratory Animals* sets standards for diverse laboratory animal care and use practices. It frames its standards as performance, engineering, and practice standards, with a strong emphasis on performance standards, allowing for multiple routes to clearly defined outcomes. Standards intended to be upheld rigorously are indicated through the use of *must* in the description, and those accommodating more flexibility are indicated through *may* and *should* statements. With respect to pain management standards, a fourth type of standard—the jurisdictional standard—has been prevalent through all 8 editions of the *Guide*. Under jurisdictional standards, specific methods and outcomes for measuring, preventing, or alleviating pain are not detailed, but the various jurisdictions of veterinarian, investigator, and IACUC are elaborated. Although data on pain management in laboratory animals has expanded greatly since the 1996 *Guide*, the eighth (2011) edition does not contain major new standards or guidance regarding animal pain management. Requirements for veterinary and IACUC involvement remain as in prior editions, and the duty of veterinarians and scientists to stay abreast of new developments is expected to drive refinement of animal pain management institution by institution. The current article details selected specific pain management standards in the 2011 *Guide*, lists topics in pain management for which the *Guide* does not set clear standards, and suggests possible standards for those topics.**

**Abbreviation:** OLAW, Office of Laboratory Animal Welfare.

First published in 1963 as the *Guide for Laboratory Animal Facilities and Care*,[5] the *Guide for the Care and Use of Laboratory Animals* (the *Guide*) has since served as a reference on laboratory animal care and use throughout the world. Two panels of 31 experts spent more than 2 years in producing the eighth edition[28] for publication in 2011. This serious effort reflects the equally serious role of the *Guide*: for funded institutions, the United States Public Health Service "requires institutions to use the *Guide* as a basis for developing and implementing an institutional program for activities involving animals,"[34] whereas AAALAC uses the *Guide* as one of 3 primary standards for assessing institutions for accreditation. The Office of Laboratory Animal Welfare (OLAW) and AAALAC have both posted guidance on how they will use this new edition of the *Guide* to review compliance and the timetable according to which compliance is expected.[7,16]

The *Guide* serves several partially overlapping roles, providing veterinary and technical information, management recommendations, ethical norms, and regulatory requirements (for recipients of funds from the United States Public Health Service). During the updating process preceding each new edition of the *Guide*, the authoring committee of content experts, most of whom are laboratory animal veterinarians, review the available scientific information about laboratory animals, prioritizing peer-reviewed scientific publications. These reviewers determine what new information about laboratory animals has been established since the previous *Guide* and use their practical experience to suggest how this new factual information should inform practices in a research institution. A second role of the *Guide* is recommending institutional arrangements and personnel policies that its authors believe, based not on scientific study but on other factors, will work best. A third role of the *Guide* is to set ethical norms. A fourth is to set regulatory standards, the minimal expectations that institutions will be required to meet for funding from the Public Health Service and the standards by which AAALAC will assess institutions that voluntarily seek its accreditation. All of these roles—technical, managerial, ethical, and regulatory—are in the current *Guide*'s discussions of animal pain management.

The Public Health Service mandate to minimize laboratory animal pain is clear: "Procedures with animals will avoid or minimize discomfort, distress, and pain to the animals."[14] Its application, however, is complicated, because 'minimize' does not equal or imply 'eliminate.' Laboratory animals risk significant pain from surgical manipulations, induced or spontaneous cancers, diseases due to their genetic makeup, and other causes. Pain in animals may be undertreated if it is not recognized, whether because of poor training, overnight periods without pain assessments, or a lack of information on signs of pain in a given species, strain, age, or situation. Pain may be undertreated for lack of effective, safe analgesics, or for poor timing, dose, or frequency of administration. Competing concerns, especially those regarding the potential for confounding effects of pain management practices on research data, may lead to animals receiving less than complete pain alleviation.[12,30] Clearly articulated standards can guide efforts at animal welfare

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and allow assessment of the pain management program by oversight bodies.

Because of its importance and complexity, animal pain management is a major component of any laboratory animal care and use program. Animal pain was addressed in the first edition of the *Guide*, although only as a component of postsurgical care, and has been addressed in each subsequent edition.[5] In companion animal veterinary practice, patient pain management can be technically challenging but ethically clear, with little argument for leaving patient pain untreated. Veterinarians must recommend and prescribe the maximal pain relief that is safe for their patients, within the constraints of client compliance and controlled substance regulations.[23] However, the situation is different in the laboratory. Because research procedures can cause pain and because both pain and the analgesics that treat it can affect research outcomes, pain management of laboratory species has never been as simple as obtaining a veterinarian's prescription for the best analgesic for the animal. Animal comfort is balanced against research needs. Balancing the research needs and animal welfare requires factual information, ethical judgment and, for difficult cases, clear rules on who makes the final decision.

Compliance with the *Guide* is required of institutions that receive funds from the Public Health Service and is assured through several routes.[14] Institutions that have filed an Animal Welfare Assurance with OLAW self-report annually their compliance with the *Guide*. Their IACUC, veterinarians, researchers, and Institutional Official interpret the *Guide* to the best of their abilities, with guidance available from OLAW. Onsite compliance audits from OLAW are rare. Institutions might therefore vary broadly in their decisions on details that are not clearly articulated in the *Guide*. Some institutions voluntarily seek accreditation through AAALAC. Site visitors scrutinize a program in great detail and bring a cross-institutional perspective that carries the potential for increasing standardization among institutions.

Understanding an institution's pain-management requirements as based on recommendations in the *Guide* requires understanding the different levels of commitment and different types of standards in the *Guide*. Standards are norms that prescribe, recommend, or prohibit some behavior and are based simultaneously on factual information and ethical values, although not every statement of standards will make the facts or values explicit.[11]

The *Guide* (on page 8) distinguishes its *must*, *should*, and *may* statements and discusses what weight each carries.[12] Institutions need to self-assess their compliance with all of the *must* statements and most of the *should* statements. AAALAC also looks closely at this distinction.[7,9] *May*, *is*, and *can* statements are numerous within the *Guide* and are to be read as "suggestions to be considered" (p 8).[12] These can be the authors' preferred way in some circumstances to meet a stated performance goal. In addition, *may* and *is* statements have been harbingers of future editions' *should* statements. For example, whereas the seventh edition of the *Guide* indicated that "Nonpharmacologic control of pain *is* often effective,"[21] the eighth edition writes, "Nonpharmacologic control of pain . . . *should* not be overlooked" [emphasis added].[28] It is too early to say what weight AAALAC or OLAW will attach to this upgrade to *should*.

The eighth *Guide* echoes the United States government's distinction between *engineering* and *performance* standards, emphasizing flexibility and professional judgment. In American policy, as explained by the United States Office of Management and Budget circular A19,[35] the difference between performance and engineering (or prescriptive, or design) standards is not how forcefully compliance is required but rather the route to compliance. A performance standard "states requirements in terms of required results with criteria for verifying compliance but without stating the methods for achieving required results."[35]

In service of the goal that animals experience no pain or distress during surgery, one could write a performance standard for surgical anesthesia, for example, that animals be anesthetized to the point of areflexia to noxious stimuli. By contrast, an engineering standard might specify a particular anesthetic and dose. Performance can be verified in real time by testing the animal's reflexes or later by reviewing anesthetic notes on patient response. Compliance with the engineering standard is verified by reviewing drug records. In this hypothetical example, the performance standard gives greater flexibility in meeting the goal of pain-free surgery. To the extent that anesthetic doses that abolish reflexes may be far higher than what is necessary to abolish pain, using areflexia as the standard risks overanesthetizing the patient, but is nonetheless clear and measureable.[6] Using an engineering standard facilitates assessment of compliance but reduces both flexibility and assurance that the goal is actually being met for the individual patient. The key issue is not whether the patient received the prescribed dose, but whether the administered dose safely abolished intraoperative pain.

As with surgical anesthesia, so too with postsurgical analgesia, although measuring painfulness in conscious animals may be more complicated than is measuring reflexes in anesthetized patients. An engineering standard might state specific drugs and dosages for a given species and a given procedure. A performance standard might state the parameters to be monitored and at what frequency and set a criterion for just how pain-free (on a given scale) an animal must be, leaving choice of analgesic flexible.

The *Guide* contains both engineering and performance standards, emphasizing the importance of flexibly met performance standards. But the *Guide* also includes what I call *jurisdictional standards*. [10] A recurring practice since the first edition of the *Guide* has been to supplement technical animal-specific information with recommendations on who in an institution should have authority or jurisdiction on various issues. Related to the jurisdictional standards are procedural recommendations and standards, such as what issues the IACUC *should* review in an animal use protocol (p 25–27).

The eighth edition of the *Guide* also has introduced, on pages xiv and 7, what it labels as *practice standards*. It does not provide specific examples, and the concept will require development, as OLAW and AAALAC develop and post their guidance on how to comply with these aspects of the eighth edition of the *Guide*.[33] Reference to practice standards seems to allow for and to require that professionals remain abreast of emerging information and that they apply this information to their facilities. However, the concept as described mostly seems to be an explanation that the performance and engineering standards listed in the current *Guide* come not just from published literature but also from experts' experience. The concept of practice standards in the eighth edition of the *Guide* is not sufficiently clear currently to formulate specific guidance to facilities in preparing for accreditation site visits.

## Standards of Animal Pain Management in the *Guide*

What are the current *Guide*'s standards of animal pain management, and how can AAALAC or IACUC assess com-

| Statements including *must* or *essential* | Page |
|---|---|
| Veterinary consultation must occur when pain or distress is beyond the level anticipated in the protocol description or when interventional control is not possible. * | 5 |
| If the responsible person (for example, investigator) is not available or if the investigator and veterinary staff cannot reach consensus on treatment, the veterinarian must have the authority, delegated by senior administration and the IACUC, to treat the animal, remove it from the experiment, institute appropriate measures to relieve severe pain or distress, or perform euthanasia. * | 114 |
| Some species may mask signs of pain until they are quite severe. It is therefore essential that personnel caring for and using animals be trained in species-specific and individual clinical, behavioral, physiologic, and biochemical indicators of well-being. | 121 |
| The proper use of anesthetics and analgesics in research animals is an ethical and scientific imperative. | 120 |
| **Statements including *should*** | |
| Reduction should not be a rationale for reusing an animal or animals that have already undergone experimental procedures especially if the well-being of the animals would be compromised. * | 5 |
| If multiple survival surgery is approved, the IACUC should pay particular attention to animal well-being through continuing evaluation of outcomes. | 30 |
| Whether a procedure is major or minor should be evaluated on a case-by-case basis, as determined by the veterinarian and IACUC. * | 30 |
| When attempting to categorize a particular surgical procedure, the following should be considered: the potential for pain and other postoperative complications; …* | 117 |
| It should be considered that procedures that cause pain in humans may also cause pain in other animals. | 120 |
| The selection of appropriate analgesics and anesthetics should reflect professional veterinary judgment. | 120 |
| After recovery from anesthesia, monitoring is often less intense but should include attention to basic biologic functions of intake and elimination and to behavioral signs of postoperative pain . . . | 120 |
| Nonpharmacologic control of pain may be effective and should not be overlooked as an element of postprocedural or perioperative care for research animals. * | 122 |
| Monitoring includes routine evaluation of anesthetic depth and physiologic functions and conditions, such as body temperature, cardiac and respiratory rates and pattern, and blood pressure, and should be appropriately documented. * | 119 |
| Studies that may result in severe or chronic pain or significant alterations … should include descriptions of appropriate humane endpoints or provide science-based justification … * | 5 |
| Determination of humane endpoints should involve the principal investigator, the veterinarian, and the IACUC, and should be defined when possible before the start of the study. * | 27 |
| **Statements including *may*, *is*, or *can*** | |
| *Recognition and Alleviation of Pain in Laboratory Animals* is an excellent source of information about the basis and control of distress and pain. * | 120 |
| Use of balanced anesthesia, including the addition of an intraoperative analgesic agent, can help minimize physiologic fluctuations during surgery. | 119 |
| Preemptive analgesia (the administration of preoperative and intraoperative analgesia) enhances intraoperative patient stability and optimizes postoperative care and well-being by reducing postoperative pain. * | 119 |
| Analgesia may be achieved through timely enteral or parenteral administration of analgesic agents as well as by blocking nociceptive signaling via local anesthetics (for example, bupivacaine). * | 119 |
| Commercially available opiate slow-release transdermal patches or implantable analgesic-containing osmotic minipumps may be useful for [chronic pain] relief. * | 120 |
| When novel studies are proposed or information for an alternative endpoint is lacking, the use of pilot studies is an effective method for identifying and defining humane endpoints. * | 28 |
| Alleviation of chronic pain may be more challenging than postprocedural pain; commercially available opiate slow-release transdermal patches or implantable analgesic-containing osmotic minipumps may be useful…* | 122 |

**Figure 1.** Selected standards relevant to pain management in the eighth edition of the *Guide for the Care and Use of Laboratory Animals*. *, statement new to the eighth edition of the *Guide.*

pliance? Figure 1 lists several standards regarding animal pain management; some overlap with the management of distress, whereas others are focused more specifically on pain. Readers expecting specific guidance on pain recognition, prevention, or management will not find them in the *Guide*. There are no tables of recommended drugs and dosages comparable to those for cage size and ambient temperature. Whereas Chapter 3 specifies clear measureable performance criteria for cage size (for example, on page 56, that "at a minimum, animals must have enough space to express their natural postures and postural adjustments without touching the enclosure walls or ceiling, . . ."), there is nothing similar with respect to pain. The standards tilt instead primarily—but not exclusively—to the jurisdictional, mostly without defined or measureable performance criteria.

**Jurisdictional standards.** The eighth edition of the *Guide* continues principles that have been maintained throughout previous editions, placing pain management squarely in the realm of veterinary medical care (and thereby requiring every institution to have at least a part-time veterinarian). After passage of the 1985 Health Research Extension Act,[21] the seventh issue of the *Guide* updated how IACUC, veterinarians, and investigators interact. The current issue of the *Guide* continues to consider protocol-associated pain management a component of veterinary medical care (p 120), although it is the IACUC, not the veterinarian, that approves a protocol and its pain management provisions. However, when the approved protocol leads to more pain or distress than anticipated, the investigator *must* contact the veterinarian (p 5).

A new provision under *Emergency Care* in the eighth edition of the *Guide* (p 114) stipulates that in an animal health emergency when the investigator is not available, the veterinarian must have authority "delegated by senior administration" to treat an animal in need. Of note, this emergency veterinary authority extends to situations when the principal investigator is available but is not in consensus with the veterinarian on the appropriate treatment. This expansion of the veterinarian's authority (and moreover, this recognition that such disagreements can arise) is new to the current *Guide*. This expanded authority of the veterinarian does not presently extend outside of emergency situations, where the IACUC retains its authority. Based on components of the current *Guide*, AAALAC's new Program Description form for accreditation specifically asks what authority the Attending Veterinarian has for handling animal emergencies.[9]

**Other personnel issues: training and qualifications.** Staff training has been a concern since the first edition of the *Guide*. The eighth edition of the *Guide* continues this theme with no significant changes, highlighting that it is *essential* (which seems stronger than *must*) that people caring for animals be trained on recognizing species-specific and individual indicators of wellbeing (p 121). Site visitors could assess this need as an engineering standard (by looking at training records) or as a performance standard (by observing outcomes and determining whether poor outcomes reflect insufficient training).

**Sources of external guidance.** In addition to referencing specific laws that must be abided, the *Guide* points readers to other sources of guidelines (which may meet the definition of 'practice standards'), such as those for biosafety concerns and animal euthanasia, that should or must be followed.[4,13,14] AAALAC underscores these documents' importance by listing them in its *Reference Resources* for accreditation.[7] In its discussions of pain, the current edition of the *Guide* references several documents, including the National Research Council's 2009 *Recognition and Alleviation of Pain in Laboratory Animals*,[15] as sources of information. None of these is listed as a document that *should* or *must* be consulted, nor is the National Research Council report one of AAALAC's posted reference resources. Therefore, institutions may have considerably more flexibility in setting standards *in loco*, with the potential for increased interinstitutional variability in animal pain management. Institutions may differ widely in their expectation of preemptive postsurgical analgesia, in allowing various procedures (for example, tissue collection for genotyping) without anesthesia, or in their practices for permitting withholding of analgesics during painful procedures, and yet all might be compliant with the eighth edition of the *Guide*.

**Ethical positions.** The *Guide* has long included various normative, ethical positions that cannot be derived from science alone. In 1972, the fourth edition of the *Guide* highlighted multiple major survival surgeries in the same animal (except when a necessary part of a single project) for special prohibition, specifying what might constitute adequate ethical justification (for example, "conserving members of a rare species") and what would not ("cost alone").[24] The current *Guide* continues this ethical prohibition, adding the requirement for special permissions from the USDA or IACUC and keeping the commitment of monitoring how animals are faring "through continuing evaluation of outcomes" (p 30). On this subject, the current *Guide* has updated its standard of what constitutes a "major" surgery, combining performance criteria (including the potential for postoperative pain [p 117]) with a jurisdictional assignment (IACUC and veterinarian [p 30]) to replace older, more rigid definitions that could either under- or overscore how 'major' a procedure might be to the animal. Surgeries that previously were classed as minor might now be classed as major and vice versa.

The issue of when to allow multiple surgery is a subset of a broader long-running ethical concern in laboratory animal use: the balance of refinement compared with reduction of animal numbers.[40,41] The current *Guide* updates its stance on this issue, urging less intensive use of more animals rather than more intensive use of fewer animals: "Principal investigators are strongly discouraged from advocating animal reuse as a reduction strategy, and reduction should not be a rationale for reusing an animal or animals that have already undergone experimental procedures, especially if the well-being of the animals would be compromised" (p 5). This norm could apply to surgical or nonsurgical uses. The *Guide* generally has not explained its reasoning on these issues in depth, but in this balance of numbers compared with harm-per-animal, scientific reasoning is less likely at play than are basic ethical principles, such as fairness.

**Technical guidance.** The *Guide* does contain some specific recommended or required practices, although the jurisdictional recommendations nonetheless predominate. Compared with the level of detail in the *Environment, Housing, and Management* chapter, for example, detailed technical recommendations on pain management are sparse. Veterinarians are expected to stay current with evolving information and standards of care, as presented in emerging research studies, at conferences and symposia, and in assorted textbooks.[1-3,17-20,22] If they look to the *Guide* for technical or medical guidance on veterinary practice for pain management, they will learn that: (1) the use of balanced anesthesia, including intraoperative analgesics, can minimize physiologic fluctuations during surgery (p 119; new to the eighth edition of the *Guide*); (2) pain is assessed by behaviors, which may vary with species (p 120); (3) pre- or intraoperative preemptive analgesia reduces postoperative pain (p 121); (4)

analgesics may be either systemic or local (p 121; new to the eighth edition of the *Guide*); (5) patches and slow-release pumps may be useful for some chronic pain (p 122; new to the eighth edition of the *Guide*); and (6) painful stimuli can return a lightly anesthetized animal to consciousness, that antinociceptive doses of anesthetics are required to prevent this, and that checking a single reflex response may be insufficient to assess this (p 122; new to the eighth edition of the *Guide*). Some of these *can* and *is* statements have associated *should* statements in the current edition of the *Guide*. Others (for example, discussions of balanced anesthesia, preemptive analgesia, and the use of patches and pumps for long-term analgesia) do not have the status of *should* in the current edition.

So what should institutions do to stay compliant with the *Guide* regarding pain management? In addition to some longstanding general principles (for example, adequate training, assuming that what is painful in people might be painful to animals) and the jurisdictional commitments noted earlier: (1) animals should be monitored for postoperative pain, for infection, and for return to function (intake, elimination; p 120); (2) postoperative monitoring should include wound management and timely removal of sutures, clips, or staples (p 120); (3) animals should be monitored for pain even after administration of pain medicines and should receive additional pain treatment if necessary (p 122; new to the eighth edition of the *Guide*); (4) nonpharmacologic pain management strategies should be considered (p 122; new to the eighth edition of the *Guide*); (5) antinociceptive depth of anesthesia must be checked prior to starting surgery (p 122; new to the eighth edition of the *Guide*); and (6) anesthetic doses should first be defined by doing a procedure without paralyzing agents before doing it with muscular blockade (p 123).

The preface to the eighth edition of the *Guide* preface notes increased coverage of intraoperative monitoring (p 119) and that readers are advised to read and interpret, looking for the implied *should*. Because routine monitoring of blood pressure and even respiratory rates is difficult in mice and is all but impossible with fish or frogs, professional judgment is necessary. That said, the current *Guide* promotes a higher standard of intraoperative care than used previously, with its emphases on maintaining body temperature, replacement of fluid losses, and more extensive monitoring than those indicated through the less specifically worded "physiological function . . . and clinical signs" of the seventh edition of the *Guide*.[27]

The current issue of the *Guide* has likewise greatly expanded the discussion of humane endpoints as a strategy for limiting animal pain and distress. The emphasis is on defining endpoints early in the process (during protocol development), as a collaboration among veterinarian, principal investigator, and IACUC (p 27–28). Pilot studies are recommended for some situations, as are recommended readings on setting appropriate endpoints. Models most likely to require endpoint-setting are listed (p 27) with a general suggestion that physical or behavioral deficits or tumor size might serve as endpoints (p 123); more specific technical design or performance standards (for example, tumor diameter of 2 cm or greater or a tumor that interferes with mobility) are not provided.

## Guidance on Specific Facets of Animal Pain Management

Despite the expanded coverage, especially in details on anesthetic monitoring and setting endpoints, and despite specific jurisdictional recommendations on management of perioperative and chronic pain, the eighth edition of the *Guide* has relatively little content on the technical and veterinary aspects of animal pain management. This limited content may reflect a lack of available information or professional and cross-institutional consensus on best practice, with a belief that the *Guide*'s should not drive minimal standards. The following sections discuss some aspects of pain management that are not covered extensively in the Guide.

**Chronic pain.** Chronic pain is a serious concern in laboratory animal medicine. This pain may be the direct result of studies of chronic pain or may accompany spontaneous arthritides, cancers, or other natural illnesses. Contingent pain that is caused by experiments (for example, cancer studies) but is not a necessary or intended part of the experiment is a significant welfare problem.

Moderate chronic pain can be challenging to diagnose. Cancer, joint, and other chronic pains in human and nonhumans are often refractory to analgesic treatments.[29] Moreover, if the experiment itself is the source of the pain, pain management strategies that do not negatively interfere with the study are required. The eighth edition of the *Guide* and the National Research Council's *Recognition and Alleviation of Pain in Laboratory Animals*[15] agree that monitoring for the earliest possible endpoints is crucial, but in the face of myriad models that may cause chronic pain, both publications stop short of setting specific design or performance standards.

The current *Guide* mentions 2 possibilities for analgesic management of chronic pain: transdermal opiate patches and implantable osmotic pumps containing analgesics (p 122). At present, this one-sentence mention seems arbitrary in highlighting these 2 modalities and is of limited use. Other considerations include size limitations (opiate patches that are suitable for small rodents are not presently available), slow-release NSAID or lidocaine patches, issues related to the need for multiple surgeries to place and replace osmotic pumps, the availability of oral pain medications for long-term use, and consideration of the negative effects of pain and analgesics on animal health and on some types of research, whether from chronic pain or from the available treatments

**Category E studies.** Studies that are reported in column E on annual USDA reports (that is, studies for which the IACUC approves withholding of pain management in animals that will undergo more than minor or momentary pain or distress) generate major animal welfare concerns. The same issues arise for non-USDA-regulated animals, even if study is not designated as category E. Category E studies are not limited to pain research but may include a wide range of cancer, toxicology, inflammatory, or infectious disease research. The fourth and fifth editions of the *Guide* had clear and simple jurisdictional statements indicating that if such studies must be done, they must be directly supervised by the responsible investigator.[24,25] The sixth edition of the *Guide* added the requirement for committee approval.[26] The seventh and eighth editions of the *Guide*, despite their expanded discussions of what IACUC review, are not explicit regarding whether category E studies must be reviewed or might be approved. Therefore, clear guidance—be it ethical, jurisdictional, or technical—is presently unavailable.

The National Research Council's publication on pain[15] emphasizes that pain itself, not just analgesics, can cause unwanted variability in research data. Therefore a reasonable standard for approval of category E studies might be the requirement for a literature search for the effects of both pain and analgesics on the model. Such literature searches might generate no useful information, but this suggested standard coupled with more

comprehensive reporting of animal research,[29,31] could influence publication practices. An IACUC must determine how to proceed if necessary information on effects of pain and pain treatments is incomplete or not provided. A model-by-model review, suggesting which analgesics are acceptable and which are disruptive, could be helpful but likely would require far more detail than the *Guide* could include. Currently, institutions may vary greatly in what they consider to be a category E study and in what justification is necessary for its approval.

For euthanasia (as called for in Public Health Service Policy[14]) and for biosafety, the *Guide* sets standards by referring to other expert documents. The National Research Council publication on pain[15] could serve this role with regard to pain. The document contains some fairly explicit standards,[15] including that (1) analgesic use should be timed so that effective plasma levels are achieved when nociceptive barrage is greatest (p 72); (2) untreated pain should not be used to restrain animals from moving and injuring themselves postoperatively (p 76); (3) postoperative pain management should not rest solely on the residual effects of intraoperative anesthetics with analgesic effects (p 76); (4) analgesics should be excluded from studies of inflammation only if other factors that affect inflammation or immunity are well controlled (p 89); and (5) standard manipulations and husbandry procedures should be modified for hyperalgesic animals in chronic pain to less painful procedures (p 97).

## Conclusion

In the 14 y since the publication of the seventh edition of the *Guide*, the literature on laboratory animal pain detection and treatment has grown. Veterinary standards of practice for pain management have evolved.[1-3,23] The effects of pain and of analgesics on various research models have been investigated and published (for example, in studies of tumor metastasis).[32,37-39] The eighth edition of the *Guide* reflects this evolution indirectly by emphasizing that veterinarians and scientists must stay current with this literature rather than by providing specific updated medical or technical standards. Few explicit new commitments for pain management are detailed in the current *Guide*, beyond expanded consideration of humane endpoints. To comply with the new Guide, institutions already familiar with the jurisdictional standards of the seventh edition of the *Guide*, with its requirements for IACUC oversight and veterinary input, may require implementation of expanded veterinary authorization for management of emergencies but will otherwise be well situated to comply with the guidelines and mandates of the current *Guide*. The resource *Recognition and Alleviation of Pain in Laboratory Animals*[15] supplements the factual guidance provided in the eighth edition of the *Guide* and includes expert recommendations of standards that an IACUC (or the ninth edition of the *Guide*) might adopt.

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