

Comments of The Humane Society of the United States
In Response to the USDA *Federal Register* Announcement of July 10, 2000
Docket Number 00-005-1
Animal Welfare; Definitions for and Reporting of Pain and Distress
November 6, 2000

These comments are being submitted on behalf of The Humane Society of the United States (HSUS) and our more than 7.5 million members and constituents. The HSUS applauds the U. S. Department of Agriculture (USDA) for initiating its effort to revise the regulation and reporting of pain and distress in laboratory animals. We thank the USDA for giving us the opportunity to comment on these issues. Defining “distress” and implementing a more effective reporting system will help reduce animal suffering in the short term and will be important steps toward fulfilling the long-term goal, shared by animal protectionists and scientists alike, of eliminating all significant pain and distress in laboratory animals. We also believe that the USDA’s intended changes will help Institutional Animal Care and Use Committees (IACUCs) and researchers to better address pain and distress issues, and that this, in turn, will lead to better science.

The USDA’s announced plans address an issue of considerable public importance. Public concern for the suffering of laboratory animals led to the passage of the Laboratory Animal Welfare Act (later renamed the Animal Welfare Act) in 1966 and its subsequent amendments. Such concern remains high today. In a 1999 survey of the American public conducted for The HSUS, 74% of the 803 respondents either strongly opposed or somewhat opposed research that is painful to animals (Peter D. Hart Research Associates, unpublished). Similarly, 70% of the respondents in a recent survey of the British public indicated that they “can only accept animal experimentation so long as there is no unnecessary suffering to the animals” (Aldous, Coghlan, and Copley, 1999). In the same survey, when pain, injury or illness was said to be present in a hypothetical animal research scenario, support for the research dropped by 20-25 percentage points.

While not widely appreciated, scientists’ support for animal research also appears to drop significantly when animal suffering is involved. Support for animal research among American psychologists and psychology students declines by 43 to 50 percent (depending on the species of animal used) when the research involves pain and death (Plous 1996a, 1996b). These and other surveys indirectly provide powerful support for the USDA’s proposed plans.

The HSUS’s comments are organized as follows:

- I. Comments on the USDA’s Specific Questions.
- II. Comments on Concerns Raised in Other Submissions.
- III. Concluding Comments.

I. Comments on The USDA’s Specific Questions

The following comments address the specific questions posed in the USDA’s *Federal Register* announcement.

- 1. Would adding a definition of distress to the regulations help institutions using animals for research, testing, or teaching better recognize, minimize, and report animal distress?**

The HSUS steadfastly believes that adding a definition of “distress” to the regulations *will* help institutions to better recognize, minimize, and report animal distress, for the following reasons:

The absence of a definition of “distress” inadvertently provides a subtle message to institutions that the USDA is less concerned about distress than it is about pain, which discourages institutions from expending the same effort (or any effort) in tackling distress as in addressing pain.

If the USDA simply defines “distress,” that alone—quite apart from the specifics of the definition—would signal to institutions that a new era in the regulation of pain and distress was beginning, one in which distress would be expected to be tackled with the same vigor as is pain. Currently, much less attention is paid to mitigating distress than to pain. This was well illustrated at the May, 2000 Scientists Center for Animal Welfare conference on lab animal pain and distress. The HSUS’s Dr. Andrew Rowan gave a presentation in which he exhorted the scientific community to pay more attention to distress. During the question and answer session, an audience member who heads a scientific organization and serves on an IACUC stood up and complained that her committee has spent years trying to reduce pain and now The HSUS wants to double their workload by having them also tackle distress.

Similarly, a Washington University representative states in the university’s submitted comments that the “alleviation of pain is the main goal, not documenting the distinction between pain and distress.” This statement is another indication that IACUCs and researchers are not fully complying with the current USDA mandate to minimize distress as well as pain. Issuing a definition of “distress” would serve to educate and prod institutions in this direction.

Distress may be caused by pain but it is distinct from pain and can be caused by other aversive situations; therefore the current regulations—with their focus on pain—provide little guidance to institutions on tackling distress.

The current USDA regulations provide an operational definition of “pain”: “a painful procedure is defined as any procedure that would reasonably be expected to cause more than slight or momentary pain and/or distress in a human being to which that procedure is applied.” No definition is provided for “distress” or “distressful procedure.” The USDA’s definition of “painful procedures” includes those procedures that cause distress, so one could argue that this definition actually is a definition of painful or distressful procedures. In fact, the U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training provides a similar operational definition of “pain” and “distress”: “Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals” (Principle IV).

Although distress and pain often interact at the cognitive-emotional level, distress is functionally and physiologically distinct from pain. Animals can experience distress as a result of painful stimuli, but they can also experience distress as a result of a variety of stimuli and emotional states that do not cause pain (e.g. fear, boredom, illness, restraint, thirst). The administration of analgesics will not eliminate distress caused by fear or illness and yet such non-pain induced distress is arguably more widespread in laboratory protocols than physiological pain. Therefore, mitigating pain alone will not necessarily mitigate distress. The USDA needs to take action to encourage IACUCs and others to move in this direction.

Distress, like pain, is a more complicated phenomenon and concept than it initially appears to be, so institutions would be well-served by being provided with a uniform definition of “distress”, especially one that distinguishes it from related concepts such as stress.

Stress and distress are related but distinct concepts. Carstens and Moberg (2000) have defined stress as “the biological responses an animal exhibits in an attempt to cope with a threat to its homeostasis.... No stress occurs unless the animal perceives a threat, either consciously or unconsciously” (p. 65). The threat to homeostasis is considered a stressor. Stress becomes distress when the stressor is “severe, of long duration, or characterized by the cumulative effects of several stressors” and leads to the diversion of biological resources that are essential to an animal’s well-being (Carstens and Moberg, 2000). Several submissions to the USDA confuse the concepts of stress and distress (see our section “Defining ‘Distress’ Not Helpful” in Part II of our comments), which argues for the need for clarification by and guidance from the USDA.

Distress involves the activation of neural pathways in the limbic system that process emotional responses to pain, fear, anxiety and other adverse states. Since animals are non-verbal and cannot describe their feelings, distress can be assessed only by indirect measures. Given this limitation, and the relatively small degree of attention given to understanding the welfare implications of stress in laboratory animals, there are currently few methods that have been applied in identifying and reducing the distress caused to animals in research. Two operational systems are described in the proceedings of the Zeist conference on humane endpoints (Hendriksen and Morton, 1999).

Pain has been studied extensively and guidelines for pain research have been developed by organizations such as the International Association for the Study of Pain. None of the other aversive stimuli (with the possible exception of tumor biology - see Workman et al. (1998)) has been similarly addressed by the relevant scientific societies. There are indications that distress and pain have been and are overlooked - especially in non-verbal humans or animals. For example, surgery on human neonates was typically performed without general anesthesia before the mid-1980s (Bouwmeester, van Kijk & Tibboel, 1998). The fact that human infants could not speak and describe their feelings was probably a contributing factor to the overlooking of neonatal pain and suffering. Similarly, The HSUS believes that a significant amount of the pain and distress of (non-verbal) laboratory animals is overlooked and/or its severity discounted. Any action by the USDA concerning pain and distress will be the first step towards eliminating this inattention.

If the USDA defines “distress” and steps up its attention to distress mitigation, this regulatory activity would inevitably stimulate discussion and research on this phenomenon, which would aid institutions in tackling distress.

In biomedical research, animals may experience discomfort, anxiety, and fear in addition to functional deficits caused by experimental procedures. In most experimental protocols, an animal's pain may be treated with anesthesia and analgesics. These measures may relieve or even eliminate the experience of pain. To date, however, there are no similarly well-known methods to alleviate the distress, anxiety, and fear an animal is subject to before, during, or after experimental procedures. There is both an animal welfare and a scientific need to understand animal distress and fear, and their relationship to pain.

The HSUS recognizes that the systematic reduction of animal distress (and pain) in the research laboratory is, for several reasons, not a trivial task. (That is why The HSUS has suggested a 20-year timeframe to achieve the goal of eliminating significant laboratory animal pain and distress.)

First, there is much conceptual confusion in the use of terms such as pain, distress and suffering, and how they relate to one another. Most of the relevant literature concentrates on pain, not distress or suffering. Second, animal use in the laboratory is quite varied; refinements developed for any one specific procedure do not necessarily translate to other procedures. Third, animal distress (and pain) is not easy to recognize or measure unambiguously and there is considerable opportunity for legitimate disagreement among scientists. Sensitive, practical measures to gauge levels of distress in common laboratory animal species do not presently exist. For the most part, animal care staff rely on *ad hoc* observations that have little empirical support (e.g. “the animals looked fine”) to ascertain whether animals are experiencing pain and/or distress. Fourth, there is limited published information about animals’ experience of distress (and pain) caused by typical laboratory procedures.

If principal investigators, lab personnel, and IACUCs do not currently have the tools to document distress objectively, or do not recognize distress caused by disease, toxic agents or psychological factors, then it is unlikely that they will take action to alleviate such distress when it occurs. It is therefore essential to promote research and discussion on when distress occurs and to achieve some consensus on those procedures that cause either pain or distress. It is not beyond the scope and responsibility of the scientific community to determine underlying principles of distress alleviation in animals that can then be applied to the varied research models and methods.

We strongly believe that, if the USDA defines “distress” and steps up its attention to distress mitigation, this regulatory activity would inevitably stimulate discussion and research on this phenomenon, which would aid institutions in tackling distress. There are parallels between the USDA’s actions on the issue of psychological well-being of primates and its proposed actions on distress. The USDA’s definition of psychological well-being in the mid- to late-1980s, and the implementation of the associated regulations, engendered an enormous increase in discussion and research on this issue. Defining “distress” is likely to elicit a similar reaction. The USDA has an important opportunity to spur progress in this arena.

Other reasons

There also are other reasons why the USDA should define “distress,” apart from whether or not such action would help institutions to better recognize, minimize, and report distress. Because distress can adversely affect scientific results (e.g. ILAR, 1992), any regulatory action that encourages greater attention to distress is likely to improve the quality of data derived from animal research. This will have the end result of improving the cost-effectiveness and health impact of biomedical research.

Also, the Organization for Economic Cooperation and Development (OECD, 2000) is about to release its guidance document on humane endpoints, which includes definitions of “distress” and other key terms. The emerging international standardization on pain and distress issues now requires that the USA evolve its regulatory systems to harmonize them with those of other OECD countries, especially those in Europe.

2. If a definition for distress is created, what elements should be included in the definition?

Moberg and Carstens’ (2000) state that distress “occurs when the biological cost of stress negatively impacts biological functions critical to the animal’s well-being” (p. 65). This

characterization refers to when distress might be expected to occur but it does not provide an operational definition. ILAR (1992) provided the following operational definition of “distress”: “an aversive state in which an animal is unable to adapt completely to stressors and the resulting stress and shows maladaptive behaviors” (p. 4). However, this definition refers only to overt behavior, which is too limiting.

Animals attempt to maintain homeostasis and any threat to homeostasis can be considered a stressor. “If a stressor is severe or prolonged, then the total biological cost of the stress response may require the diversion of resources from other biological activities” (Moberg, 1999). Therefore, when normal biological function is threatened, the animal experiences distress and its welfare is threatened.

Animals experience a range of stressors both in the wild and in the laboratory. Such stressors are not necessarily harmful and may produce changes in the physiological, biochemical and behavioral parameters that tend to return the individual animal to a state of homeostasis (cf. Carstens & Moberg, 2000). Distress occurs when such stressors are severe, of long duration, or both, requiring an animal to mobilize significant biological resources in order to attempt to return to normal. Such states of distress are characterized by changes that include (but are not necessarily limited to) one or more of the following: significant weight loss (more than 15% in 24 hours or a steady weight loss of 2-4% a day for several days in a row), massive mobilization of the flight or fight response requiring more than 12 hours to recover, chronic maladaptive behavior, a significant change in body temperature (1.5 degrees or more), or what might be characterized generally as the obvious display of "sickness" behaviors and changes (e.g. Gregory 1998). These endpoints should be considered interim suggestions that may be modified as our empirical knowledge grows.

The HSUS further argues that some of the measures that are now commonly used to determine whether laboratory animals are in distress, such as looking for evidence of reduced activity during the day, are inadequate. On average, the level of activity of a mouse or rat during the "lights on" phase of laboratory housing is only about 5% of the level of activity during the "nocturnal" phase. Thus, it is difficult in the “lights on” phase to determine whether an animal is in distress simply from observations at a distance because differences in activity between well animals and ill animals are going to be relatively small. Research institutions should not necessarily have to follow a set of proscribed rules for determining distress but should be required to establish a program of action that they will institute to monitor the level of pain and distress that animals might be experiencing. Such a plan should be part of the annual filing by each institution so that Congress and the public (whose taxes constitute such a large proportion of animal research support) can determine whether each research institution at least has a proposed plan for assessing and minimizing both distress and pain.

Distress is related to the *emotional content* of noxious experiences that elicit physiological stress responses in animals, whether that noxiousness is predominantly emotional (e.g. fear), predominantly physical (e.g. vigorous exercise) or a combination of both (e.g. pain) (David Mellor, personal communication to The HSUS, 2000).

The term “pain-induced distress,” whether referring to the consequences of injury caused by husbandry practices, or in clinical settings, is used to indicate that the physiological responses reflect the interacting emotional and physical facets of the noxious experience.

“Distress” is perhaps best defined as an aversive state resulting from an inability to adapt to stressors or from maladaptation (OECD, 2000). Stressors are physical or behavioural disturbances of the immediate environment. Distress is usually associated with a change in motility or

locomotion, and can result in stereotype behaviour. The major stressors associated with distress are those that induce pain, fear or anxiety. An example of distress is a negative behavioural change in anticipation of a repetitive, unpleasant experimental procedure, as when an animal retreats to a corner of the cage and struggles and vocalizes excessively when seized.

We recommend that the USDA adopt a definition of “distress” that includes several operational endpoints and then provide examples of procedures that might cause distress. There is a surprisingly limited amount of published knowledge about how to determine when animals experience distress, and how much suffering is caused by typical laboratory procedures (Rowan et al., 1998). Therefore, more data are needed to discriminate amongst research models and specific techniques in terms of the distress they typically induce and to respond to public concerns about such distress.

Policy #11 currently provides three examples of procedures that may cause more than momentary or slight distress:

- Food or water deprivation beyond that necessary for normal presurgical preparation.
- Noxious electrical shock that is not immediately escapable.
- Paralysis or immobility in a conscious animal.

This is an extremely limited set of possible examples. We would suggest that the USDA identify both research areas and research techniques where animal distress might be expected to occur. Institutions can then use these lists to guide the development of policies to minimize or eliminate distress in such areas. The following is an incomplete list of research models/research areas in which the animals used might be expected to experience non-pain-induced distress:

- aggression models
- anxiety models (e.g., Vogel conflict-drinking model)
- cancer (tumor burden, cachexia, therapy, carcinogenicity testing)
- depression models (e.g., learned helplessness, forced swimming, infant separation)
- diabetes models
- drug addiction and withdrawal models
- environmental stress models (e.g., hot, cold)
- fear models
- immunological research (e.g., vaccine potency testing)
- infectious disease
- motion sickness models
- nutrition research
- panic models
- pharmacology (some) (e.g., Tumor Necrosis Factor, capsaicin research)
- psychopathology (other than anxiety, fear, depression, etc., mentioned above)
- radiation research
- stress models (psychological)
- toxicology (induced effects)
- transgenic research

As suggested by several other commentators, the USDA should foster the development of a catalog of distress behaviors, postures, and clinical signs pertaining to each species. Examples of

such putative distress indicators may include vocalizations, loss of appetite, self-mutilation, and long-term lethargy.

Comprehensive clinical monitoring (and recording of clinical signs) contributes to the detection of early signs of distress. The USDA should encourage detailed clinical “scoring” (as opposed to simply writing that an animal “looks sick”). Detection of early signs is the key issue for both animal welfare and good science.

Baumans et al. (1994) developed a set of guidelines for assessing mild, moderate and severe distress based on clinical signs (Table 1). This table should not be used as a hard and fast rule, but it does provide some suggestions of what should be looked for and how to classify an animal demonstrating these signs.

Table 1: Approaches to Classifying Distress.

Factors viewed from a distance	Mild	Moderate	Severe
Behavior	Interacts with peers Hunched for short period Transient vocalization Transient tremors No convulsions	Little peer interaction Hunched intermittently Intermittent vocalization when provoked Intermittent tremors Intermittent convulsions	Hunched persistently (“frozen”) “Distressed” vocalization when unprovoked Persistent tremors Persistent convulsions
External appearance	Partial piloerection No prostration No self-mutilation	Staring coat—marked piloerection Transient prostration (<1 hr) No self-mutilation	Staring coat—marked piloerection Dehydration—skin tenting Prolonged prostration (1 hr) Self-mutilation
Factors viewed while handling			
Provoked behavior	Subdued but responsive, normal behavior pattern	Subdued behavior even when provoked	Unresponsive to extraneous activity or provocation
Body weight and food consumption	Reduced weight gain Food and water consumption is 40-75% normal for 72 hr.	Weight loss up to 20% Food and water consumption is less than 40% normal for 72hr.	Weight loss greater than 25% Food and water consumption is less than 40% for 7 days or is no consumption for 72 hr.
Clinical signs	Normal Respiration Transient oculo-nasal discharge	Intermittent abnormal breathing Persistent oculo-nasal discharge	Labored respiration Persistent and copious oculo-nasal discharge

The HSUS suggests that the USDA recommend this system for assessing and classifying distress, with the following modification. There is a difference between weight loss that results from acute procedures (such as surgery under general anesthesia in which post-operative weight loss is due largely to lack of food and fluid intake) and a slow but steady loss in weight (or a lack of weight gain in a growing animal). We suggest that a rapid weight loss of more than 15% should be regarded as a sign that an animal is experiencing distress. A steady loss of weight of as little as 2-3% over a week should also be regarded as a sign that an animal may be experiencing distress. Reliable methods for scoring animal distress provide experimenters with the ability to make semi-quantitative assessments and thereby to assess the efficacy of any proposed refinement (Lloyd and Wolfensohn, 1999).

We believe that weight loss holds promise as an indicator of stress and distress. However, much more data must be collected to determine, for example, what percent of weight loss (and over what period) indicates moderate or severe distress.

3. What are the benefits and limitations of our pain and distress classification system?

The USDA requires each research facility using regulated animals to fill out and submit an annual report form to the agency. The form lists the types of regulated animals down the rows of the left hand side (e.g., dogs, cats, and nonhuman primates) and calls for the numbers of animals used in research to be placed in various columns (categories) according to whether or not the animals were considered likely to experience pain or distress and whether or not drugs were used to alleviate such pain and distress.

The precise wording of the current pain and distress categories on the form is as follows:

- **Category C:** Number of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress or use of pain-relieving drugs.
- **Category D:** Number of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic or tranquilizing drugs were used.
- **Category E:** Number of animals upon which teaching, experiments, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic or tranquilizing drugs would have adversely affected the procedures, results or interpretation of the teaching, research, experiments, surgery or tests. (*An explanation of the procedures producing pain or distress in these animals and the reasons such drugs were not used must be attached to this report.*)

The wording given in Policy 11 for these same categories is slightly different and is as follows (re-formatted here to use the same format as above):

- **Category C:** Individual animals that do not experience pain/distress from testing procedures.
- **Category D:** Individual animals experiencing pain/distress which is alleviated with anesthetics, analgesics, sedatives and/or tranquilizers. This category includes terminal surgery under anesthesia.
- **Category E:** Individual animals in which needed anesthetics, analgesics, sedatives, and/or tranquilizers are withheld. For all column E animals, a written justification, approved by the IACUC, must be provided, including CFR (Code of Federal Regulations) references or other guidelines if appropriate.

Benefits of the Current Pain and Distress Classification System

Although the current pain and distress classification system has been heavily and justifiably criticized (see below), it has a few modest benefits over no system at all. First, the system calls attention to pharmacological agents (e.g., anesthetics) that can be used to reduce pain and distress. It could be argued that this regulatory spot-lighting has encouraged research personnel to use such agents, particularly during the early years of the classification system when the use of analgesics, sedatives, and tranquilizers was not as common as today. Second, the current system requires that facilities provide a description of category E protocols and an explanation of why pain- and distress-relieving agents were withheld. This has enabled the USDA and interest groups to analyze these descriptions and explanations, and to identify the types of research that account for the bulk of category E studies (e.g., Stephens et al., 1998).

Limitations of the Current System

Andrew Rowan, then of Tufts University, organized a meeting in 1995 to discuss the USDA pain and distress classification and what might be done to modify it. All of the approximately forty representatives of animal research and animal protection organizations present agreed that the current classification scheme was unhelpful and ambiguous and needed to be modified in some way (Rowan, 1996).

There are several limitations to the current pain and distress classification system:

- A. There is no category for procedures causing pain and distress that are partially, but not fully, alleviated by the administration of drugs. Thus, one institution might report a protocol in which the animals receive anesthesia but experience some post-operative pain or distress as Category D (the animals received drugs) whereas another might interpret the same procedure as Category E (the animals experienced pain or distress).
- B. A careful reading of Categories D and E reveals that animals who experience pain and distress, and who do not receive drug relief for reasons other than likely interference in the research, do not have a classification category. This provides a legalistic loophole which is being exploited by at least one research institution.
- C. The categories do not adequately address the issue of levels of pain and distress. The current system does not address the intensity or duration of pain and distress, the effectiveness of the relief, nor the timeliness of the relief. The system boils

down to a yes/no dichotomy: pain or distress did not occur (Categories C and D) and pain or distress did occur (Category E). Category E alone is a hodgepodge of procedures causing some unspecified level of pain or distress. Thus, the current system is not a true pain or distress scale. Consequently, the scientific community does not have a means of identifying commonly used procedures that cause severe pain and distress. In contrast, many countries distinguish between minor, moderate, and severe pain/distress in their scales (see below).

- D. The current system does not adequately address the issue of distress. On the annual report form, Category C mentions pain-relieving drugs but not distress-relieving drugs. None of the categories mentions non-pharmacologic mitigation of distress, such as through modifications of husbandry and management practices, socialization and handling, environmental enrichment, and experimental design (see ILAR, 1992).
- E. The current pain and distress categories are confusing, a problem confounded by the limited guidance from the USDA on how to complete the annual report forms. The confusion stems in part from the problems identified in items A, B, and C above. Also, many observers are confused by the current wording of Category D, which, according to Policy 11, refers to animals experiencing pain and distress, yet the pain and distress are said to be alleviated. So, did the animals actually experience pain and distress and, if so, was it fully alleviated? Similarly, according to the wording on the annual report form, Category D refers to procedures involving accompanying pain and distress for which appropriate pharmacological relief was provided. Again, did the animals actually experience pain and distress and was it completely alleviated? Some institutions classify pain and distress prospectively, others use retrospective reporting. Some institutions classify all animals in a protocol in the same category, others apportion the animal numbers into two or three categories depending on whether the animals were part of experimental or control groups. As a result of all the confusion, institutions interpret and complete the forms in their own ways, rendering interpretation all the more difficult.
- F. For the following reasons, the information reported in the annual reports is far from comprehensive, may be unreliable, and needs to be interpreted with some caution (e.g. Welsh, 1991).
 - 1. Research facilities are not required to disclose their use of lab-bred rats and mice, as well as any birds, reptiles, amphibians and fish. Total use figures for the United States can only be estimated. These groups of animals account for an estimated 90% or more of all (vertebrate) animal use. The National Institutes of Health (NIH) report mouse and rat use voluntarily and, in 1997, these two species accounted for 97% of the 762,398 animals reported used by NIH.
 - 2. The USDA reporting categories of "wild", "farm" and "other" animals have changed since 1972 and cannot be used to track trends. The numbers are now reported under the categories "farm" and "other."
 - 3. Individual reports to the USDA vary in their thoroughness and accuracy, and some institutions may not be included in the annual compilation

simply because their reports were submitted late. This problem has been addressed in recent years and the Annual Reports are now more complete and also more accurate.

Given these many problems, it is not surprising that The HSUS has uncovered widespread inconsistencies and underreporting of research animal pain and distress. An HSUS analysis of the annual statistics on animal use for recent reporting years revealed enormous (and unexplained) variation from state to state in the reporting of animals used in painful procedures without the administration of pain-relieving drugs. There are some evident differences in the types of research performed from state to state; however, the variations are much more likely to be due to differences in the way the USDA forms are interpreted from state to state. There are also curious variations within the same state over time. From 1983 to 1991, Virginia reported an average of 10-30% of the animals used in Column E but for 1993, 1995 and 1996, the percentage in Column E was under 1%. Arkansas reported little or no use of animals in Column E for a number of years, and then in one year, 1993, there was a jump to 56%. For 1994, 1995, 1996 and 1997 the numbers bounced around from 21% to 0% to 0% and then back up to 36%. For these and other reasons, many commentators have understandably hesitated to draw firm conclusions from the USDA figures (e.g., Orlans, 1993).

Recent statistics from Switzerland, the Netherlands, and Canada indicate that approximately 30% to 45% of research animals experience moderate to severe pain and distress, whereas the comparable U.S. numbers (Category E) average only about 10%. This discrepancy suggests that pain and distress are underreported in the U.S. system. The most direct evidence for the underreporting of animal suffering comes from reports of individual research institutions. The top fifty research institutions (based on NIH-funding) reported a total of only 0.6% of regulated animals used in 1996 and 0.8% in 1997 as experiencing pain and distress (Category E). These discrepancies appear to be largely the result of the shortcomings of the U.S. reporting system, rather than on differences in alleviation of pain and distress or the lack of figures on non-regulated species in the U.S. (lab-bred mice and rats, as well as birds, reptiles, amphibians and fish).

The current statistics reported to the USDA and available to the public may not only be giving interested observers an erroneous picture of the current situation and recent trends. It may also provide a false sense of security for those who use and care for laboratory animals. If IACUCs and laboratory personnel continue to use an ambiguous and ill-defined reporting system to claim few research animals are suffering, their level of attention to the recognition and alleviation of pain and distress will be diminished.

4. Should our pain and distress classification system be revised or replaced? If so, what specific modification or alternate classification systems should we consider?

The HSUS strongly recommends that the USDA transform its current classification system into a graded scale of pain and distress that reflects levels of severity (sometimes termed “invasiveness”). Such severity scales are in use in several countries, including Canada, Finland, The Netherlands, New Zealand, Switzerland, and United Kingdom. The simplest of such systems has three levels: minor, moderate, and severe. It should be noted that several countries have a more comprehensive system than is being proposed here (see Appendix A). For example, The Netherlands requires that the duration of pain be indicated and categorized, and New Zealand uses a five-level grading system.

While The HSUS would welcome the USDA’s adoption of a three-level system (minor, moderate, and severe), The HSUS recommends a four-level system that is a slight variation on the minor, moderate, and severe scheme. We recommend that the minor category be subdivided into two categories, depending on whether minor pain and distress resulted from a truly benign procedure or from the application of pain- or distress-relief during a procedure that might have otherwise resulted in moderate or severe pain and distress (see Table 2). Thus, the recommended system has some continuity with the current system, with its focus on pain- and distress-relief. However, the moderate and severe categories are not subdivided based on the presence or absence of pain/distress-relief. The committee that devised this system (see below) believed that any proposed new system with more than four categories would be too burdensome on the scientific community.

Table 2: Proposed new classification scheme.

Category	Pain and/or Distress	Anesthesia/ Analgesia	Full IACUC Review	Alternatives Literature Search
I	Minor or None	No	<i>No</i>	<i>No</i>
II	Minor or None	Yes	<i>Perhaps</i>	<i>Perhaps</i>
III	Moderate	Yes or No	<i>Yes</i>	<i>Yes</i>
IV	Severe	Yes or No	<i>Yes</i>	<i>Yes</i>

This recommended classification scheme was developed and supported by an eight-member committee consisting of representatives of animal research and animal protection organizations. The committee was chaired by Dr. Andrew Rowan, then of Tufts University, and included an observer from the USDA (Dr. Jerry Depoyster). The committee conducted its work during the mid-1990s and submitted its recommendation to the USDA in 1997. It is important to emphasize that this proposed pain scale is not a product of The HSUS but of the expert working group.

While the proposed system continues to address pain relief (Categories I and II), it also emphasizes a key issue in laboratory animal welfare and in the public controversy over animal research: the *levels* of pain and distress actually experienced, whether or not analgesics or anesthetics are used. This additional information could be used to monitor trends in pain and distress across institutions and over time and could provide data for comparisons with countries with similar systems. Also, IACUCs could use the new system to gauge the intensity of the review needed for proposed research, with protocols in the severe category being assigned the most intense review. Following the trends in the severe category would inevitably lead to a focus on how procedures in that category could be refined in order to be placed in the “moderate” category and, perhaps, ultimately in the “minor” category. This would lead to a true focus on the Three Rs of replacement, reduction, and refinement, as Policy #11 intends.

If the USDA adopted the system depicted in Table 2, the agency could offset the burden of imposing a new system upon the research community by waiving the requirements for full IACUC review of protocols and for an alternatives literature search, for protocols in Category I (and perhaps II).

Any meaningful pain and distress classification system should recognize that there are methods of relieving suffering other than the use of anesthetics and analgesics. For example, antibiotics could be used to reduce any distress and discomfort associated with an infectious disease.

See Appendix A for information on how selected countries' classify and report pain and distress. Please note that several of the countries have included examples with the definition of each category.

5. Should animal pain and distress be prospectively or retrospectively reported?

Prospective reporting would be less burdensome than retrospective reporting. Researchers and IACUCs could simply assign a pain and distress category at the time of protocol review. On the other hand, retrospective reporting would be more accurate, given the uncertainties of predicting experimental outcomes. The HSUS recognizes that whatever reporting system is adopted will be a compromise between accuracy and expediency.

In this light, The HSUS recommends that the reporting system should be based primarily on prospective assessments, but that these should be revisited when the anticipated category is an under- or over-estimate of pain and distress. (In fact, IACUCs should ask for routine reports of animals in distress from the animal care staff. Such reports are valuable indicators of potential problems for the IACUC and also serve to send a positive signal to the animal care staff that animal pain and distress is a serious issue that it (the IACUC) wishes to know about.) A post-hoc accuracy check recognizes that many different procedures could be minor, moderate, or severe depending on how they are carried out (reflecting, for example, the training and skill of the laboratory personnel, the conditioning of the animal to the procedure in question, the health status of the animal, and the specifics of the procedure).

A post-hoc accuracy check would be essential in cases where outcomes are largely unpredictable, such as in much of toxicity and efficacy testing and in the generation of transgenic strains.

This variability in pain and distress outcomes argues not only for a retrospective accuracy check, but also for some degree of monitoring and scoring of animals during and after experimental procedures. Such scoring will document the extent to which the animals' physiology and behavior deviate from normal. This documentation can then be used to retrospectively check the prospective pain and distress classification and also to support the final decision regarding classification.

In New Zealand, the researchers anticipate the expected severity in their applications to the Animal Ethics Committees. Then, on occasion, they are required to report back once the experiment has progressed to a certain stage. This is particularly useful when the anticipated severity is found to have been either over- or under-estimated.

II. Concerns Raised by Other Commentators

The HSUS has reviewed hundreds of comments submitted to the USDA on this docket. In this section, we address the major concerns of those commentators who oppose the changes that the USDA is proposing. Although we address their specific stated concerns, we note at the outset that the organized biomedical community has opposed every attempt at changing whatever the current status quo might have been in the regulation of animal research. That same community has

typically then later gone on to embrace these regulatory changes and use the presence of such regulations as evidence of their concern for animal welfare. Typically, new regulations have turned out not to be as onerous as originally claimed by opponents of any change. It is certainly true that the IACUC system involves obvious costs that were not part of animal research prior to 1985 but the system can also be argued to have produced benefits to both science and to the animals. The benefits to science (better protocols, healthier animals) are not as obvious or easy to quantify but that does not mean they are unimportant or insignificant.

Going Beyond Statutory Authority

The president of the Federation of American Societies of Experimental Biology (FASEB) stated in her comments that “[t]he current pain and distress reporting system already goes beyond the intent of Congress as expressed in the Animal Welfare Act, and USDA should not seek further expansion of regulatory requirements.” Many other commentators also expressed the same view. It is ironic that these commentators did not challenge the USDA over the reporting system throughout the more than 20 years during which it has generated fairly limited and questionable data. Only now, when the USDA proposes to generate meaningful data, are there complaints. The possibility of adding a fourth category to the system hardly qualifies as a burdensome expansion of regulatory requirements.

The USDA’s statutory authority to require reporting of pain and distress statistics stems primarily from Section 13 of the Animal Welfare Act, as amended in 1970 (Public Law 91-579) and 1985 (Public Law 99-198—December 1985). The specific provisions are as follows (skipping irrelevant provisions):

Section 13. (a) (1) *“The Secretary shall promulgate standards to govern the humane handling, care, treatment, and transportation of animals by dealers, research facilities, and exhibitors.”*

(a)(3) *“In addition to the requirements under paragraph (2), the standards described in paragraph (1) shall, with respect to animals in research facilities, include requirements—“*

(A) *for animal care, treatment, and practices in experimental procedures to ensure that animal pain and distress are minimized, including adequate veterinary care with appropriate use of anesthetic, analgesic, tranquilizing drugs, or euthanasia;*

(B) *that the principal investigator considers alternatives to any procedure likely to produce pain to or distress in an experimental animal;*

(C) *in any practice which could cause pain to animals...(ii) for the use of tranquilizers, analgesics, and anesthetics; (iii) for pre-surgical and post-surgical care by laboratory workers, in accordance with established veterinary medical and nursing procedures;.....and*

“(E) that exceptions to any such standards may be made only when specified by research protocol and that any such exception shall be detailed and explained in a report outlined under paragraph (7) and filed with the Institutional Animal Committee.”

“(7)(A) The Secretary shall require each research facility to show upon inspection, and to report at least annually, that the provisions of this Act are being followed and that

professionally acceptable standards governing the care, treatment, and use of animals are being followed by the research facility during actual research or experimentation.”

“(B) *In complying with subparagraph (A), such research facilities shall provide*

- (i) information on procedures likely to produce pain or distress in any animal and assurances demonstrating that the principal investigator considered alternatives to those procedures;*
- (ii) assurances satisfactory to the Secretary that such facility is adhering to the standards described in this section; and*
- (iii) an explanation for any deviation from the standards promulgated under this section.”*

[Section 21 reads as follows:]

“The Secretary is authorized to promulgate such rules, regulations, and orders as he may deem necessary in order to effectuate the purposes of this Act.”

[Finally, section 25 reads as follows:]

“No later than March of each year the Secretary shall submit to the President of the Senate and the Speaker of the House of Representatives a comprehensive and detailed written report with respect to—

- (1) the identification of all research facilities, exhibitors, and other persons and establishments licensed by the Secretary under section 3 and section 12 of this Act;*
- (2) the nature and place of all investigations and inspections conducted by the Secretary under section 16 of this Act, and all reports received by the Secretary under section 13 of this Act*

In light of the above AWA provisions, we believe the USDA does have the statutory authority to continue or modify the current pain and distress classification system. USDA Deputy Administrator Dr. Ron DeHaven acknowledged the USDA’s authority in this regard: “Congress made clear their intent to minimize animal pain, distress, and discomfort in the 1985 amendment to the Animal Welfare Act. References to minimizing or eliminating pain are found in Section 13 of the Animal Welfare Act. In this section, Congress mandated the Secretary of Agriculture to promulgate regulations to ensure that animal pain and distress are minimized” (DeHaven, 1998).

For more information about the history of USDA regulations pertaining to annual reports, see Appendix B. For current regulations regarding the annual report, see Appendix C.

In summary, it is clear that the AWA places a significant emphasis on determining the extent of animal pain and distress in animal research and in encouraging efforts to limit such pain and distress. The 1985 amendments, in particular, emphasized the need to address pain and distress.

Increasing Time and Paperwork Burden

The main worry of the scientific community is that a revised pain and distress classification system will result in a substantially increased paperwork burden. One commentator, the Colorado Serum Company, conducted a “hypothetical analysis” that estimated that adding a new category to

the three-category reporting system would more than double the time necessary to comply with the system. The primary reason provided was that “a veterinarian will have to re-evaluate each animal procedure to determine which categories the procedures fall under.” This comment speaks to the issue of the time commitment needed to learn a new system. However, a veterinarian (or other IACUC member) already has to classify the proposed experiments and a new category should help to clarify the systems, rather than confuse it further.

Once researchers and IACUCs are familiar with any new classification system, it is not clear why assigning a protocol to one of four categories would take more time than assigning a protocol to one of three categories. Moreover, the USDA may decide to revise the nature of the categories but otherwise stay with a three-category system. In this case, there would be a short-term time commitment necessary to learn the new system. This is the case for any sort of upgrade in the workplace, whether it concerns a new computer program, phone system, or cage-washing system. However, there would be no long-term time commitment above current requirements. One could even argue that revising the current system, with all its ambiguities and deficiencies, will result in a DECREASE in time commitment.

Similarly, many commentators have argued that not only would a new classification system require more of a time commitment, but also more paperwork per se. If the USDA adopts a revised classification system with three categories, it is not clear how paperwork would be increased, either with respect to protocol review forms or annual report forms. If the USDA moves to a four-category system, it is not clear why adding a fourth tick-box to a protocol review form would add extra pages to the form. One could argue that adding a fourth column to the USDA annual report might translate into an extra page, but surely the USDA could redesign the form to maintain the single-page format.

Defining “Distress” Not Helpful

Many commentators claim that a regulatory definition of “distress” would not enhance the ability of institutions to recognize, minimize, or report animal distress. The HSUS disagrees and discussed four reasons for our position in our answer to USDA’s question #1. We will not repeat those arguments here. Instead, we will discuss weaknesses in the comments of those who argue against defining “distress.”

Many commentators point to the existing confusion over the meaning of distress and related terms. For example, one commentator stated: “An additional obstacle to defining distress is that the term overlaps with numerous other terms used in the scientific literature and general discourse, e.g., suffering, pain, stress and discomfort. These terms, including distress are frequently used indiscriminately and even interchangeably, resulting in bewildering ambiguity over the precise meanings of each.” We agree that there is much confusion over the use of these terms in the scientific literature and discourse. However, the solution is not to let this confusion linger, but to define these terms. Without a definition of “distress,” how can researchers and IACUCs fulfill their regulatory obligation to minimize distress? Indeed, many of the commentators from the scientific community inadvertently imply that they have not been addressing animal distress in the laboratory, contrary to the mandate in both the Animal Welfare Act and the directions in the resulting regulations.

The American Physiological Society’s submission notes the “lack of scientifically validated measures of pain and distress.” Given that the USDA has been responsible for addressing the problem of animal pain and distress since 1970 and its mandate was greatly expanded in 1985, The HSUS believes that this statement simply demonstrates the lack of attention of the scientific

and regulatory community to the issue despite the legislative mandates to do something. Defining “distress” will help rectify this situation.

Many of the submitted comments do not adequately distinguish between stress and distress. Many mention distress when it appears that they are actually referring to stress. For example, a representative of Washington University stated “any handling of an animal constitutes distress to the animal.” In FASEB’s submission, president Dr. Mary Hendrix claims that “[d]istress cannot be readily defined because it is not a discrete state. Rather, there is a continuum of stress that may be caused by physiological, psychological or environmental factors. Stress responses are integral to life and in some cases may even help animals adapt.” Clearly the USDA should distinguish stress from distress in any new regulations. We agree that stress is integral to life and cannot be eliminated from life. However, in a carefully controlled environment that is completely defined by its human managers, distress is not necessary, integral or desirable.

Revising the Pain and Distress Classification System Will Not Improve Animal Welfare

Many commentators claim there is no point in revising the pain and distress classification because the animals themselves will not benefit. They see the reporting system as a time-consuming, bureaucratic exercise with little if any redeeming value. While we agree that the **current** reporting system has limited value given its shortcomings (see our answer to USDA question #3 above), we believe strongly in the value of a meaningful pain and distress reporting system..

The HSUS believes that a meaningful pain and distress reporting system has the following benefits:

It sensitizes all parties-- including researchers, IACUCs, granting agencies, and regulatory agencies-- to the issue of pain and distress,. The current discussion about pain and distress has already had the effect of focusing more attention on studies that are likely to cause distress due to factors other than pain. More knowledge of what may constitute distress cannot but help to improve laboratory animal welfare.

It helps researchers, IACUCs, and granting agencies make a more accurate cost/benefit analysis of proposed research by encapsulating the expected “cost” of the research to the animal subjects (e.g., moderate pain and distress) (see U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training #2).

It can be used to focus the attention of researchers and IACUCs on refining protocols classified as severe.

Conversely, it can be used to expedite IACUC reviews of protocols classified as minor.

It can be used to focus the attention of USDA inspectors on severe protocols.

It can inform all interested parties, including concerned members of the public, about the current situation and recent trends in laboratory animal pain and distress. For the first time, the reporting system will be meaningful enough to bring genuine accountability to the issue of how institutions deal with pain and distress issues, and, human nature being what it is, accountability will bring improved animal welfare.

It can be used by organizations that fund research and development of alternative methods to allocate their limited resources only to severe protocols.

It can be used to make comparisons to the situation in other countries.

Classifying Specific Procedures

Many commentators have indicated that all euthanasia protocols should be categorized as “column C.” The HSUS disagrees. Each such protocol should be evaluated against the criteria of whatever classification system the USDA adopts. Some so-called “euthanasia” protocols can involve pain or distress (e.g. the kill traps permitted in the latest AVMA Euthanasia report) and therefore do not belong in Category C under the current system. There is also evidence that the use of CO₂ for euthanasia can cause distress under some exposure regimens; therefore we oppose an automatic classification of CO₂ euthanasia under “column C.” However, in general, we agree that protocols in which animals are carefully handled, and then studied either under terminal anesthesia or killed to provide tissues, should not be categorized as experiencing moderate or significant pain and/or distress.

Leaving decisions to the IACUCs

Many commentators have opined that determinations regarding the classification of pain and distress should be left to the individual IACUCs. It is likely that IACUCs will be the entities making the final classification decisions at each institution. However, their discretion pertains to the choice of category, not the type of reporting system that should be used. The reporting system would be the official system adopted by the USDA. Moreover, the USDA should strive to develop consistency among institutions in how they report similar procedures. The vagueness and ambiguities of the current system have generated confusion. For example, some institutions report toxicity studies as column D procedures, while others categorize them as column E. This sort of inconsistency undermines the whole rationale of having a reporting system.

III. Concluding Comments

The HSUS believes the time is right for the USDA to upgrade the regulation and reporting of pain and distress in laboratory animals. The IACUC system has been in place for over a decade and has had an incubation period in which to begin to tackle the major issues associated with protocol review and program review, including the prevention and alleviation of pain and distress. We recognize that the IACUC system has made important strides in this connection. However, much more can and should be done.

We estimate that the issue of tackling distress in laboratory animals is about ten to fifteen years behind where we are today in tackling pain, both in terms of attention to the issue and in terms of our technical sophistication in recognizing, quantifying, and alleviating this adverse state. Given this situation, we would argue that distress is a bigger factor in compromising the welfare of laboratory animals today than is pain. The USDA bears part of the responsibility for this, in not defining “distress” in the thirty-four year history of the AWA.

We applaud the USDA for seeking to help rectify this situation. As argued above, defining “distress” will not only provide guidance to laboratory personnel and IACUCs, it will also signal the agency’s determination to see that animal distress is given the attention it deserves.

The agency should leverage the impact of a new definition of “distress” by also taking the following steps:

- provide the research community with clear and numerous examples of procedures that cause distress;
- require greater training for laboratory personnel in the recognition and alleviation of distress;
- promote a broad discussion of the procedures that cause distress, the levels of distress caused, and the means to preventing and alleviating distress; and
- foster the development of a catalog of distress behaviors, postures, and clinical signs exhibited by each laboratory species (examples of such putative distress indicators may include vocalizations, loss of appetite, self-mutilation, and long-term lethargy).

The U.S. Government Principles for the Utilization and Care of Vertebrate Animals Used in Testing, Research, and Training, which apply to Public Health Service-supported research, provides a similar operational definition of “pain” and “distress”: ““Proper use of animals, including the avoidance or minimization of discomfort, distress and pain when consistent with sound scientific practices, is imperative. Unless the contrary is established, investigators should consider that procedures that cause pain or distress in human beings may cause pain or distress in other animals” (Principle IV). This statement is neither ambiguous nor equivocal. The USDA needs to step up its oversight of distress to better match what is already PHS policy.

In addition to defining “distress” and taking related actions, The HSUS also believes the time is right for the USDA to revise its pain and distress classification system. That system is nearly thirty years old and was last revised in 1979. Since then, it has been roundly criticized by scientists and animal protectionists alike. Given the system’s limitations, the resulting data have largely been ignored and comparisons to the situation in other countries have been largely precluded.

The effective integration of distress into the pain and distress classification system will mean that the USDA must broaden its focus beyond pharmacological approaches to the mitigation of suffering. Other approaches, including behavior and husbandry, can play an important role in reducing distress and influencing the proper classification of a protocol. This realization makes the current classification system completely unsuitable as a basis for moving forward. If, for example, lab personnel did one small act to reduce distress in an otherwise highly distressful or painful protocol, that arguably would be enough to classify the protocol in current category D—an untenable situation. A new criterion, other than the provision (or withholding) of some level of pain- or distress-relief, however inadequate, must be devised for a meaningful system.

Defining “distress” and implementing a more effective reporting system will help reduce animal suffering in the short term and will constitute important steps toward reaching the long-term goal, shared by animal protections and scientists alike, of eliminating all significant pain and distress in laboratory animals. The HSUS will do its part to work towards helping to reach this goal by pursuing our Pain and Distress Initiative (see Appendix D).

We firmly believe that the investment in tackling pain and distress, as reflected in the USDA’s intended changes, will not only promote animal welfare, but also lead to better science. It is now axiomatic that animals experiencing fear, depression, or other forms of distress can yield skewed research results.

The HSUS makes the following specific recommendations.

- A. The USDA should establish a definition for “distress.”
- B. A definition of “distress” should include the following elements:
1. language that distinguishes between stress and stressors (part of normal living) and “distress;”
 2. language that distinguishes between pain, fear, anxiety, illness, and “distress” to ensure that it is recognized that “distress” is not simply a synonym for pain but is much more;
 3. language that provides some practical guidance on suitable endpoints that indicate when distress might be expected to occur. Such endpoints could include weight loss (distinguish between acute and rapid weight loss followed by recovery and chronic situations where weight is either not gained or is lost slowly (1-2% a day) but steadily), body temperature changes (either an increase or decrease), behavior (provoked or normal), and physiological indicators such as stress hormones, heart rate, respiratory rate, etc.
- C. The USDA should modify the current pain and distress classification to eliminate the current ambiguities and to establish a three- or four-tier system build around the concepts of minor, moderate and substantial suffering. Reporting for this system should initially be prospective but it is recommended that IACUCs be encouraged to seek routine (monthly) reports from animal care staff that identify animals that are experiencing distress. These retrospective reports will help to improve the accuracy of the prospective predictions.
- D. The USDA should require all institutions to submit, as part of their Annual Report, a written description of the program they have instituted to address how they are meeting the Congressional mandate to minimize animal pain and distress in research and testing. Such a program could include the use of scoring sheets, animal care monitoring and reports back to the IACUC, specific programs to address distress that cannot be treated by the use of anesthetics or analgesics, etc.
- E. For all protocols classified as substantial, the USDA should require descriptions of the procedures and detailed and referenced justifications as to why the animals’ pain and distress could not be reduced further, which would be comparable to the existing reporting requirements for Category E procedures.
- F. The USDA should ensure that its inspectors are thoroughly familiar with the new distress guidelines and they should make reporting standards for experimental protocols an essential part of each facility inspection.

References

Aldous, P., Coghlan, A. and Copley, J. (1999). Let the people speak. *New Scientist* 162 (2187): 26-31.

Baumans, V., et al. (1994). Pain and distress in laboratory rodents and lagomorphs: Report of the FELASA Working Group on Pain and Distress. *Laboratory Animals* 28:97-112

Bayvel, A.C.D. (1999). The New Zealand regulatory approach to the use of live animals in research, testing and teaching. Paper presented at the Third World Congress on Alternatives, 29 August – 2 September, 1999, Bologna, Italy.

Bouwmeester, J., van Dijk, M., and Tibboel, D. (1998). Human neonates and pain. *Humane Endpoints in Animal Experiments for Biomedical Research: Proceedings of the International Conference, 22-25 November 1998, Zeist, The Netherlands* (Hendriksen, C.F.M. & Morton, D.B, eds), pp.20-25. Laboratory Animals Ltd & The Royal Society of Medicine Press: London, UK.

Bundesamt fur Veterinarwesen. (1999). Tierversuche in der Schweiz. VfV: Bern, Switzerland.

Carstens, E. and Moberg, G. (2000). Recognizing pain and distress in laboratory animals. *Institute for Laboratory Animal Research* 41(2): 62-71

de Greeve, P. (1999). Adverse effects: Regulation and classification in Europe. Paper presented at the Third World Congress on Alternatives, 29 August – 2 September, 1999, Bologna, Italy.

DeHaven, R (1998). Pain Management and Humane Endpoints workshop
<http://altweb.jhsph.edu/science/meetings/pain/dehaven.htm>

Federal Register (1989, March 15) Department of Agriculture, Animal and Plant Health Inspection Service, Vol. 54, No. 49

Gregory, NG (1998). Physiological mechanisms causing sickness behaviour and suffering in diseased animals. *Animal Welfare* 7:293-305.

Hendriksen, C.F.M. and Morton, D.B, eds. (1998) *Humane Endpoints in Animal Experiments for Biomedical Research: Proceedings of the International Conference, 22-25 November 1998, Zeist, The Netherlands*. Laboratory Animals Ltd & The Royal Society of Medicine Press: London, UK.

Institute of Laboratory Animal Resources. (1992). Recognition and Alleviation of Pain and Distress in Laboratory Animals. National Academy Press: Washington, DC

Lloyd M.H. and Wolfensohn S.E. (1999). Practical use of distress scoring systems in the application of humane endpoints. *Humane Endpoints in Animal Experiments for Biomedical Research: Proceedings of the International Conference, 22-25 November 1998, Zeist, The Netherlands*, (Hendriksen, C.F.M. & Morton, D.B, eds.) pp.48-53. Laboratory Animals Ltd & The Royal Society of Medicine Press: London, UK.

Moberg, G. (1999,). When does stress become distress? *Lab Animal* 28 (4/April):22-26

Organization for Economic Cooperation and Development. (2000). Draft [June] Guidance Document on the Recognition, Assessment, and Use of Clinical Signs as Humane Endpoints for Experimental Animals Used in Safety Evaluation. OECD Environmental Health and Safety Publications Series on Testing and Assessment No. 19. OECD: Paris.

Orlans, F.B. (1993). *In the Name of Science*. Oxford.: New York.

Plous, S. (1996a). Attitudes toward the use of animals in psychological research and education: Results from a national survey of psychologists. *American Psychologist* 51:1167-1180

Plous, S. (1996b). Attitudes toward the use of animals in psychological research and education: Results from a national survey of psychology majors. *Psychological Science* 7:352-358

Purves, K. (2000). Global harmonization of pain and distress classification systems: Current analysis and opportunity for change. *Journal of Applied Animal Welfare Science* 3 (1): 49-62

Rowan, A.N. (1996). AWA classification of pain and distress in animal research: A proposal. Unpublished proposal submitted to the USDA.

Rowan A.N., Stephens, M.L., Dolins, F., Gleason, A. and Donley, L.. (1998). Animal welfare perspectives on pain and distress management in research and testing. *Pain Management and Humane Endpoints*, November 2-3, 1998. [See <http://altweb.jhsph.edu/science/meetings/pain/rowan.htm>]

Stephens, M.L., Mendoza, P., Weaver, A., and Hamilton, T. (1998). Unrelieved pain and distress in animals: An analysis of USDA data on experimental procedures. *Journal of Applied Animal Welfare Science* 1 (1): 15-26.

Welsh, H. (1991). Reported animal use drops further at companies and noncommercial facilities. *News for Investors*, February: 6-9.

Workman, P., Twentyman, P., Balkwill, F., et al. (1998). United Kingdom Coordinating Committee on Cancer Research (UKCCCR) guidelines for the welfare of animals in experimental neoplasia. *British Journal of Cancer* 77:1-10.

Appendix A

Information on Pain and Distress Reporting Systems in Other Countries

Note: The following list is not exhaustive. Other countries, including Finland (F.B. Orlans, personal communication to The HSUS, 2000), also have pain and distress classification systems.

Canada

In Canada, “Categories of Invasiveness” (CI’s) are based on the invasiveness of the procedure and on the potential for pain/distress, not only on actual pain/distress. The categories are defined as the following:

- B: Experiments which cause little or no discomfort or stress
- C: Experiments which cause minor stress or pain of short duration
- D: Experiments which cause moderate to severe distress or discomfort
- E: Experiments which cause severe pain near, at, or above the pain tolerance threshold of unanesthetized conscious animals

These CI’s have been formally defined and used since 1991 but detailed data has only been provided since 1996. According to the Canadian Council on Animal Care (CCAC), the categories have been well received by the scientific and animal welfare communities in Canada, and are generally being appropriately used within Canadian institutions (Marie Bedard, CCAC, personal communication to The HSUS, 2000).

In addition, CCAC provides examples for each category. Possible examples of category D (moderate to severe distress or discomfort) are listed as:

“major surgical procedures conducted under general anesthesia, with subsequent recovery; prolonged (several hours or more) periods of physical restraint; induction of behavioral stresses such as maternal deprivation, aggression, predator-prey interactions; procedures which cause severe, persistent or irreversible disruption of sensorimotor organization; the use of Freund’s Complete Adjuvant.”

The Categories of Invasiveness and accompanying examples can be found at: <http://www.ccac.ca/english/categ.htm#d>. Note that major surgical procedures are placed in category D even when anesthesia is used. Finally, if there is a procedure that has not yet been categorized, the CCAC generally recommends that the higher category of invasiveness be used. The HSUS highly recommends the use of examples for each new category that the USDA adopts, no matter what system is implemented, in order to guide IACUCs in the reporting of animals used.

The Netherlands

The Netherlands has adopted a mild, moderate and severe categorization system. The categories are not defined, but examples are given. The categories are as follows (Purves, 2000):

- Minor (force feeding innocuous substances, killing without prior sedation, blood sampling, rectal examination, restraint pens where animals can stand or lie down).
- Moderate (skin transplants, cesarean section, catheterization).
- Severe (total bleeding without anesthesia, production of genetic effects, LD50, immunization in footpad or with complete adjuvant)

It is required that the duration of pain and whether pain prevention methods were used must be noted and the following duration categories are used: (a) less than 1 day, (b) 1-7 days, (c) 7-30 days and (d) more than thirty days.

New Zealand

New Zealand's system is a five-point scale by grade of severity of proposed procedures. Procedures placed in category #1 would be the most benign, causing no suffering, and #5 being the greatest degree of suffering that could be approved. A #5 procedure requires justification and a compelling reason for a procedure of such severity. (The original scale used an alphabetical system, which is still used by many institutions, but the text of the categories has remained the same) Furthermore, a severity rating is applied to each group of animals; therefore control animals are not given the same rating as the "treated" animals.

As mentioned above, New Zealand is the only country that lists procedures according to both duration and degree of pain, which leads to better assessments and more accurate reporting.

The following are New Zealand's categories (the "alphabetical" version, mentioned earlier) (Bayvel, 1999; Purves, 2000):

- Grade O- No stress, pain, or suffering; or virtually no stress, pain, or suffering (field studies, non-invasive studies).
- Grade A- Stress, pain, or suffering of a minor intensity for a short duration (euthanasia by electrical stunning, feeding trained animals by orogastric tube).
- Grade B- Stress, pain, or suffering of minor intensity for a long duration, or of a moderate intensity for a short duration (recovery from major surgery with effective analgesics, long-term restraint).
- Grade C- Stress, pain, or suffering of a moderate intensity for a long duration, or of a severe intensity for a short duration (recovery from major surgery without the use of analgesics, marked environmental deprivation, facial eczema, severe infectious pneumonia).
- Grade X- Stress, pain, or suffering of a severe intensity for a long duration or of a very severe intensity for any duration (LD50 toxicity testing, recovery from third degree burns).

This scale has been incorporated into a computer package used by many institutions to collate and report use of animals at various levels of severity. According to one New Zealand researcher, "the computer package works exceptionally well and greatly reduces the time commitment of institutional staff and Ministry staff who need to collate the information" (David Mellor, personal communication to The HSUS, 2000). If the USDA adopts a new set of reporting categories, the agency should consider fostering the development of a comparable software program that institutions could download.

Switzerland

Switzerland has a scale that includes categories of: none to minimal, moderate, and severe suffering (de Greeve, 1999). In 1999, Switzerland reported that 32% of the animals used in research experienced moderate or severe pain and distress (Bundesamt für Veterinärwesen, 1999).

United Kingdom

The United Kingdom uses the concept of “severity bands.” Each qualified researcher is given a license that specifies an allowable severity limit for that researcher. Therefore, some licenses are approved and given with the restriction of only allowing a moderate severity of pain and distress *limit*, for example. According to the Guidance on the Operation of the Animals (Scientific) Procedures Act 1986, “License holders are required by conditions in both project and personal licenses to minimize any pain, suffering distress or lasting harm. They should approach the limit of severity which has been authorized only when absolutely necessary to meet the specified objective” [Sections 10 (2) and 5 (5)]. This documents further states that “...procedures are regulated, even when performed under general anesthesia, if the effect on a normal conscious animal would be to cause pain, suffering, distress or lasting harm.”

Appendix B

History of USDA Annual Report Regulations

The 1970 AWA amendments were the original mandates calling for all registered research institutions file an Annual Report with the USDA. The regulations requiring an Annual Report from each institution read as follows:

"2.28 *Annual report of research facilities.*
Each research facility shall submit on or before February 1, 1973, and on or before February 1 of each calendar year thereafter to the Veterinarian in Charge in the State where registered, an annual report signed by a legally responsible official covering the previous calendar year and showing that professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, during experimentation, are being followed by the research facility during actual research or experimentation."

At that time, the Annual report included two categories:

Category C: The common names and approximate numbers of animals used.

Category D: The number of experiments conducted involving necessary pain or distress to the animals without the use of appropriate anesthetic, analgesic, or tranquilizing drugs and a brief statement explaining the reasons for the same; Provided, however, that routine procedures (e.g. injections, tattooing, and blood sampling) do not need to be reported.

By 1979, the regulatory language on the Annual Report (APHIS,1979) had been revised slightly to change the reporting year from a calendar (January to December) to a fiscal year (October to September). While the regulatory language on pain relief was unchanged, the pain and distress categories on the Annual Report forms were changed and expanded to include a category E.

The three categories were as follows:

Category 'C'-The common names and approximate numbers of animal upon which research, experiments or tests were conducted involving no pain, distress, or use of pain relieving drugs. *Provided, however,* That routine procedures (e.g., injections, tattooing, and blood sampling) do not need to be reported;

Category 'D'-The common names and approximate numbers of animals upon which experiments or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used: Provided, however, That routing procedures (e.g., injections, tattooing, and blood sampling) do not need to be reported.

Category 'E'-The common names and approximate numbers of animals upon which experiments or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs would adversely affect the procedures, results or interpretation of the research experiments, or tests and a brief statement explaining the reason the same: Provided however, That routine procedures (e.g., injections, tattooing, and blood sampling) do not need to be reported.

Following passage of the 1985 AWA amendments, the USDA published its first set of proposed regulations to implement these amendments in 1987. The USDA issued a proposed Categories of Animal Use in Research and Testing based on those already in use by the CCAC and those recommended by SCAW. The proposed scale was actually a true pain scale in that the categories included minor, moderate or severe pain or distress. These proposed regulations stimulated widespread debate and opposition. The USDA was instructed by the Office of Management and Budget to prepare a new set of regulations that were more in line with the performance standards set out in the Public Health Service policies on animal research. In 1989, a second set of regulations was published for comment and, eventually, accepted. The pain classification proposal had been dropped.

In the 1989 “Reproposed Regulations,” APHIS ended up with an approach to the Annual Report that was very similar to the pre-1985 requirements. APHIS registered concern about the previous standards because some institutions had reported animal use under Column C (“no pain”) because the pain was relieved with drugs. APHIS argued that this was improper because the relief of pain does not, in their view, make the procedure one that does not involve pain. Therefore, the annual report guidelines in VS Form 18-23 were clarified to require that painful procedures be reported as such, regardless of whether or not pain is relieved (Federal Register, 1989).

Appendix C

The Current Annual Reporting Regulations [54 FR 36147, Aug. 31, 1989, as amended at 63 FR 62926, Nov. 10, 1998]

Sec.2.36 Annual report.

(a) The reporting facility shall be that segment of the research facility, or that department, agency, or instrumentality of the United States, that uses or intends to use live animals in research, tests, experiments, or for teaching. Each reporting facility shall submit an annual report to the AC Regional Director for the State where the facility is located on or before December 1 of each calendar year. The report shall be signed and certified by the CEO or Institutional Official, and shall cover the previous Federal fiscal year.

(b) The annual report shall:

(1) Assure that professionally acceptable standards governing the care, treatment, and use of animals, including appropriate use of anesthetic, analgesic, and tranquilizing drugs, prior to, during, and following actual research, teaching, testing, surgery, or experimentation were followed by the research facility;

(2) Assure that each principal investigator has considered alternatives to painful procedures;

(3) Assure that the facility is adhering to the standards and regulations under the Act, and that it has required that exceptions to the standards and regulations be specified and explained by the principal investigator and approved by the IACUC. A summary of all such exceptions must be attached to the facility's annual report. In addition to identifying the IACUC-approved exceptions, this summary must include a brief explanation of the exceptions, as well as the species and number of animals affected;

(4) State the location of all facilities where animals were housed or used in actual research, testing, teaching, or experimentation, or held for these purposes;

(5) State the common names and the numbers of animals upon which teaching, research, experiments, or tests were conducted involving no pain, distress, or use of pain-relieving drugs. Routine procedures (e.g., injections, tattooing, blood sampling) should be reported with this group;

(6) State the common names and the numbers of animals upon which experiments, teaching, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which appropriate anesthetic, analgesic, or tranquilizing drugs were used;

(7) State the common names and the numbers of animals upon which teaching, experiments, research, surgery, or tests were conducted involving accompanying pain or distress to the animals and for which the use of appropriate anesthetic, analgesic, or tranquilizing drugs would have adversely affected the procedures, results, or interpretation of the teaching, research, experiments, surgery, or tests. An explanation of the procedures producing pain or distress in these animals and the reasons such drugs were not used shall be attached to the annual report;

(8) State the common names and the numbers of animals being bred, conditioned, or held for use in teaching, testing, experiments, research, or surgery but not yet used for such purposes.

Appendix D

The HSUS's Pain and Distress Initiative

In order to help encourage a more systematic approach to pain and distress management, The HSUS has launched the Pain & Distress Initiative, which seeks to eliminate all significant pain and distress in laboratory animals by the year 2020. Eliminating animal suffering in the laboratory is an ambitious target. What is needed along the way is a focused, urgent effort to recognize, alleviate and prevent such suffering, so that science can progress without causing pain and distress to animals.

The Pain & Distress Initiative consists of four components:

1. Development of a detailed, referenced technical report on animal pain and distress by an international group of experts. The topics that will be covered by the report includes:
 - a. Definitions of pain, distress, discomfort, anxiety, fear and suffering
 - b. The biology of pain and distress
 - c. Recognition of pain and distress: current and potential approaches
 - d. Alleviation of animal pain and distress
 - e. Housing issues
 - f. Pain and distress caused by specific techniques and research endpoints
2. Outreach to Institutional Animal Care and Use Committees (IACUC's): The HSUS is seeking the cooperation and collaboration of the scientific community—those who will ultimately develop the techniques and implement the approaches that will make animal research pain and distress-free. The HSUS has sent five mailings to the chairs of over 1600 IACUCs nationwide through March, 2000.
3. Regulatory aspects: The HSUS is seeking changes to the current pain and distress reporting systems, the regulatory definition of “distress,” and the development and issuing of “best practice” guidelines covering specific techniques and research areas
4. Financial support for research on pain and distress—The HSUS plans to urge both private and government entities to fund studies aimed at developing more sensitive and practical measures of animal distress and methods by which such distress can be alleviated.

The HSUS plans to share the results gathered from the Pain and Distress Initiative with the scientific community.