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Taking Animal Welfare Seriously: Minimizing Pain and Distress in Research Animals

The Humane Society of the United States

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Minimizing Pain and Distress in Research Animals

Report prepared by the Animal Research Issues Section of The Humane Society of the United States
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THE HUMANE SOCIETY OF THE UNITED STATES
2100 L Street, NW, Washington, DC 20037
202-452-1100 • www.hsus.org

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I. Executive Summary

Both laypersons and scientists alike are uncomfortable with animal research when it causes animals to suffer. The Humane Society of the United States (HSUS) has launched our Pain & Distress Initiative to work with the scientific community to eliminate significant laboratory animal suffering by the year 2020. This goal is consistent with public opinion on animal research and with laws, regulations, and guidelines governing the conduct of animal research. While eliminating significant 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.

Polls have begun to document the influence of animal suffering on people's views toward animal research. For example, a recent poll (Aldous, Coghlan, and Copley, 1999) found that the British public's support for research on mice or monkeys declines 16% to 35% (depending on the species and field of research) when the animals are subjected to pain, illness, or surgery (factors associated with suffering). Similarly, American psychologists' and psychology students' support of animal research declines 43% to 50% (depending on the species) when asked to compare research involving caging or confinement and research involving pain and death (Plous 1996a, 1996b). The contrast between the media's (and public's) responses to two high profile cases of research in the 1980s (Baby Fae and the University of Pennsylvania Head Trauma lab) also illustrates the importance of the perceived level of animal suffering.

Public concern for research animal suffering has led to passage of two laws regulating animal research. Both laws, the Animal Welfare Act (AWA) and the Health Research Extension Act (HREA), seek to reduce any likely pain and distress experienced by research animals. Both seek to do so primarily through the establishment of Institutional Animal Care and Use Committees (IACUCs), which review in-house research proposals and periodically assess their facility's animal care and use program. Under the AWA, IACUCs are also required to ensure that researchers have searched for alternatives if their proposed animal research is likely to cause pain and distress, even if anesthetics and analgesics are used to prevent suffering. Despite its regulatory emphasis on alleviating pain and distress, the USDA provides little explicit guidance on the topic or on the potential impact of specific experimental procedures, such as infecting animals with pathogenic organisms, on animal well being.

The USDA issues annual reports that summarize data on the number of animals of regulated species used in research, testing, and education. This information is grouped under column headings that correspond to the USDA's pain and distress categories:

- procedures involving little or no pain or distress (Column C)
- pain or distress alleviated with drugs (Column D)
- pain or distress not alleviated because pain-relieving drugs would have interfered with the research (Column E)

Nationwide, about 55% of the over one million regulated animals used in research are typically reported in Column C, 35% in Column D, and 10% in Column E. In their annual reports to the USDA, research institutions are asked to describe any Column E procedures (unalleviated pain and distress) and explain why pain relieving-drugs were withheld.

The USDA's pain classification system has been criticized on several grounds. The current categories are confusing and there is no category for procedures causing pain and distress that were partially but not fully alleviated with drugs. The categories do not adequately address the issue of levels of pain and distress (the current categories boil down to a yes/no dichotomy). There is no definition for "distress" although the USDA is now working to produce one. There is no specific guidance to institutions on how to complete the annual report forms, nor is there effective USDA oversight of institutional decisions on categorization of actual experiments. It is not surprising, then, that an HSUS analysis of the annual statistics on animal use for recent reporting years reveals enormous (and unexplained) variation from state to state in the reporting of animals used in painful procedures without the administration of pain-relieving drugs.

Several foreign countries have pain classification systems that are more straightforward and meaningful than the U.S. system. Many of these systems report levels of pain and distress as minor, moderate, or severe, or some variation thereof. Recent statistics from The Netherlands, Switzerland, and Canada indicate that approximately 30% to 45% of research animals experience significant pain and distress, whereas the comparable US

numbers (Column E) average only about 10%. Similarly, the Canadians report that 13% of the animals used in the category of basic research experience moderate to severe pain. By contrast, the top fifty National Institutes of Health (NIH) funded non-profit research institutions in the US reported less than 1% of animals experiencing pain and distress in 1996 and 1997. These discrepancies appear to be largely the result of the shortcomings of the US reporting system, rather than on differences in the alleviation of pain and distress or the lack of figures on non-regulated species in the US (lab-bred mice and rats, as well as birds, reptiles, amphibians, and fish).

Pain and distress caused by specific research models and techniques raise serious concerns for those in the animal welfare community as well as in the scientific community. Yet good estimates of how much animal pain and/or animal distress is caused by particular techniques or methods are not yet available. The HSUS has compiled a preliminary list of research models and techniques that cause pain and distress. Analyses by the USDA and HSUS indicate that the majority of the animals reported in Column E are used in various testing procedures, with vaccine testing prominent among them. More data are needed to discriminate amongst research models and specific techniques in terms of the pain and distress they typically induce. Pain and distress may be specific to a particular research model, species, or gender and may affect the extent of suffering caused in that particular animal model. Such information is critical to informed decision-making by researchers, IACUCs, and others.

Despite the regulatory emphasis on alleviating pain and distress, The HSUS recognizes that the systematic reduction of animal pain and distress in the research laboratory is not a trivial task, for several reasons. 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 pain, distress and suffering are 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 or on relatively insensitive measures such as weight loss, to ascertain whether animals are experiencing pain and/or distress. Fourth, there is limited published information about animals' experience of pain, distress, and suffering caused by typical laboratory procedures. Fifth, lab personnel may develop "distancing mechanisms" that help them cope with causing harm to animals but which can also lead to people ignoring or overlooking pain or distress that, with more attention, could be alleviated or avoided altogether.

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 a 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 pain and distress alleviation in animals which can then be applied to the varied models and methods.

To help encourage a more systematic approach to pain and distress management, The HSUS has launched the Pain and Distress Initiative, which seeks to eliminate all significant pain and distress in animal research by the year 2020. The Initiative has four main components:

1. The HSUS has convened a group of experts on pain and distress to draft a comprehensive report that addresses key issues, such as the levels of pain and distress caused by common research models and techniques.
2. The HSUS is actively seeking the collaboration of IACUCs and the broader scientific community. Through mass mailings to IACUCs, we have begun facilitating an exchange of information and policies so that new ideas and initiatives, including "best practices" and "humane endpoints," can be disseminated quickly.
3. The HSUS is encouraging the USDA to adopt a new classification system that divides pain and distress into none/minor, moderate, and severe categories. Until the current USDA classification system is revised, The HSUS will seek to foster more consistency and accuracy in how pain and distress are reported.
4. 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.

As part of our efforts to raise the profile of pain and distress issues with IACUCs, The HSUS will focus on specific research areas, practices and techniques where relatively little attention has been given to animal suffering. Our aim is to seek out new approaches to recognizing, measuring, and alleviating animal distress. Also, The HSUS will encourage the NIH to issue "best practice" guidelines covering specific techniques. The HSUS urges the USDA to adopt new pain and distress categories recommended by a committee of representatives of animal research and animal protection organizations. Until a new system is in place, The HSUS recommends a number of improvements in the current system, including providing IACUCs with clear definitions and examples of levels of suffering, pain, distress, stress, and anxiety. The HSUS also recommends that:

- funding institutions provide support for refinement research
- the USDA expand regulatory coverage to birds and lab-bred mice and rats, to not only formally provide protection to these animals under the AWA, but also to gather statistics on pain and distress in these animals
- the NIH should issue "best practice" and "humane endpoint" guidelines to facilitate the pace of innovation in laboratory animal welfare

The public's support for animal use in biomedical research has declined in recent years. The decrease in support is even more evident when the public is questioned about the experimental use of animals involving pain and/or distress. Given the public's concern for the humane treatment of animals in research and our ethical obligation to the animals

themselves, there should be greater attention provided to refining techniques, to publicizing best practices, and to eliminating animal pain and distress. The HSUS Pain & Distress Initiative seeks to encourage these developments, with the goal of eliminating all significant animal pain and distress in research by the year 2020. The HSUS commends the USDA for initiating its own analysis of pain and distress reporting, and creating a proposed set of solutions for reducing animal pain and distress in a recent unpublished report.

In the past few years, fortunately, there has been an increase in attention to pain and distress issues within science and academe. These activities will lead to improvements for both animals and the humans that rely on them. In the end, better animal welfare will lead to better science, as pain and distress are eliminated and no longer have the opportunity to confound scientific data.

II. Introduction

Animal research has long stimulated concern among members of the public and the scientific community alike. While most people recognize, intellectually at least, that biomedical scientists are searching for knowledge that will improve the lot of humans and animals, the image of somebody deliberately and with careful forethought causing harm to an animal in order to produce data that may lead to some future benefit has always prompted an uncomfortable reaction outside the laboratory. As Northeastern University ethnographer, Arnold Arluke, has demonstrated so well, this discomfort is also shared by the scientists who use the animals (cf. Arluke, 1988 & 1989, and Arluke and Hafferty, 1996). However, animal research is usually justified by reference to greater benefits (new knowledge and medical treatments) over lesser costs (in animal suffering and death). One of the costs of animal research is the suffering experienced by the animals. This report provides some background to the issue of research animal suffering and describes the Pain and Distress Initiative that has been launched by The Humane Society of the United States to eliminate significant laboratory animal suffering by the year 2020 or sooner.

The goal of eliminating pain and distress in the animal laboratory is one that few, if any, people (especially scientists) would argue against, although some might question its feasibility. Public opinion surveys indicate strong concern about pain and distress in laboratory animals. Perhaps most importantly, the laws, regulations, and guidelines governing the conduct of animal research emphasize the need to minimize pain and distress. The HSUS initiative seeks to focus these concerns and policies into more urgent action to eliminate pain and distress.

While eliminating significant animal suffering in the laboratory is an ambitious target, it is certainly within the ingenuity and skills of those who use and care for laboratory animals. What is needed is a focused effort to define what is meant by animal pain and distress (no trivial task despite its apparent obviousness), to determine how we can best tell when an animal is suffering significant pain and distress, to determine what areas of research and what techniques cause such pain and distress, and then to look for

alternatives that will allow science to progress without causing such harms to animals. While laboratory animal use has fallen by approximately fifty percent in the last twenty-five to thirty years (Reduction and Replacement of animals in research) (Rowan, Loew, and Weer, 1995), there has been much less progress in the Refinement of animal use (Reduction, Replacement, and Refinement are the Three Rs of Russell and Burch (1959)).

III. Public Concerns/Attitudes

The public's perception of the levels of suffering experienced by laboratory animals used in biomedical research and testing has fueled the controversy over animal experimentation. This public concern has been translated into laws and regulations that seek to limit laboratory animal suffering, pain and distress (see Section III).
When queried, members of the general public express concerns over the treatment of non-human animals used in scientific research. In general, about 75% of the public accepts the use of animals in research while about 65% actually support the practice. Support for the use of animals changes according to the type of animal used and area of research. For example, in a 1985 poll, 88% accepted the use of rats but only 55% accepted the use of dogs. In the same poll, only 12% opposed the use of animals in medical research on cancer or diabetes but 27% opposed the use of animals in allergy testing (NABR, 1985). In another poll, 60% opposed the use of animals to test cosmetics but only 20% of the same sample opposed the use of animals to test medical products (Ward, 1990). The public is also very concerned about the treatment of research animals and a majority support a strengthening of federal regulations and the development and promotion of alternatives that will reduce animal suffering.

A recent poll, commissioned by the British magazine New Scientist, highlights the influence of animal suffering on the public's views of animal experimentation. Approval of animal research declines substantially when the experiments involve pain, illness, or surgery (see Table 1).

Table 1. Effect of public perceptions of animal pain and distress on public support for different types of animal research (adapted from Aldhous et al., 1999). Animals experience pain, illness, or surgery?	NO		YES	
	Mice	Monkey	Mice	Monkey
% approval of research to develop a new drug to cure leukemia in children	83	75	65	52
% approval for research to enable scientists to study how the sense of hearing works	70	56	36	21
% approval for research to test whether a garden insecticide will be harmful to people	56	43	29	16
	Mice		Monkeys	
Average % decline in support when animals experience pain, illness, or surgery	26%		28%	

Although the New Scientist survey was carried out in the United Kingdom, similar attitude shifts have been reported in surveys of selected samples of the American public. For example, Plous (1996a, 1996b) conducted two surveys of 5,000 randomly selected members of the American Psychological Association (APA) and 2,022 psychology students randomly sampled from 50 colleges and universities within the United States.

Both sample groups were presented with twelve different types of psychological research which required them to indicate which types of research were justified assuming "all research has been institutionally approved and deemed of scientific merit." As Table 2 shows, the majority of both graduate psychologists and psychology students did not support animal research when it caused pain or death.

Table 2. Support (% of sample) for specific research procedures among American Psychological Association members and psychology students.

	APA Members	Psychology Students
Observational Studies		
Primates	96.0%	94.8%
Dogs	89.4%	91.0%
Rats	87.3%	91.2%
Research Involving Caging or Confinement		
Primates	63.0%	57.7%
Dogs	63.4%	57.7%
Rats	77.2%	79.6%
Research Involving Pain and Death		
Primates	17.7%	10.3%
Dogs	18.8%	9.4%
Rats	34.0%	29.1%

Public uneasiness about the suffering experienced by laboratory animals is also clearly demonstrated by the different public reactions to the following two media events in the United States.

Baby Fae

On October 26, 1984 a twelve-day-old human infant with hypoplastic left heart syndrome, who came to be known to the world as "Baby Fae," received a baboon heart transplant at Loma Linda University Medical Center. Three weeks later she died of kidney failure. The operation unleashed a storm of debate and criticism. While it was generally accepted that Baby Fae was unlikely to survive for many weeks without some intervention (and even then her chances of long term survival were slim), questions were raised about the extent of the hospital's search for a heart from a human infant (although such hearts are rare) and about the lack of details on the informed consent process. Spokespersons for Loma Linda argued that the procedure was experimental therapy that offered Baby Fae her only chance at "long-term" survival. But the available data indicated that her chances of surviving for more than six months with the baboon heart were not good and several newspaper cartoons picked up on the notion that Baby Fae was just another experimental animal.

Although most of the bioethical discussion centered on whether or not Baby Fae was inappropriately used in a clinical experiment (as opposed to being provided with experimental therapy), some animal activists took the opportunity of all the media attention to criticize the use of the baboon as a donor and argued that the animal was needlessly killed. This argument was not received with much sympathy by either the media or the public. The Boston Herald captured the public rejection of the animal rights argument with an editorial cartoon which featured Baby Fae on one side and a group of animal rights activists on the other. The captions for the two sides read, "Born with half a heart"and "Born with half a brain" respectively.

Head Trauma Laboratory

Over Memorial Day weekend in 1984, members of the Animal Liberation Front (ALF) broke into a laboratory at the University of Pennsylvania Medical School. They vandalized equipment and removed sixty hours of videotapes of head injury research on baboons filmed by the research personnel (Fox, 1984). The laboratory used the baboons in experiments designed to produce non-impact (e.g. whiplash) damage to the brain and spinal chord. The animals were then studied to determine the type and extent of damage produced and the effect of the damage on the animals' subsequent behavior. The stolen items were delivered to People for the Ethical Treatment of Animals (PETA) who condensed the 60 hours down to a 25-minute videotape that raised questions about surgical and animal care standards in the laboratory.

The PETA videotape was widely distributed to the media and was discussed on a variety of popular television programs. In July 1985, the National Institutes of Health (NIH) released an interim report that concluded that the laboratory had failed to comply with stipulated animal care standards. Margaret Heckler, Secretary of the Department of Health and Human Services, did not wait for the final report. She immediately suspended the research. During this period, both the Washington Post and the New York Times ran editorial very critical of the research. The Washington Post went so far as to title its editorial "Animal Torture". Criticism of the research by print and electronic media was widespread.

These two cases - Baby Fae and the Head Trauma Laboratory - offer illustrative contrasts. When animal activists criticized the killing of the baboon in the ultimately futile attempt to treat Baby Fae's heart problem, the public and the media regarded the criticism as, at best, unfounded and misplaced. By contrast, the condemnation of the head trauma experiments by animal activists was echoed and reinforced by the media. The critical differences between these two cases that underlie the different public and media reactions are most probably the perceived differences in human benefit and animal costs. In terms of costs, the suffering of the baboon used as a heart donor for Baby Fae was perceived to be minimal or non-existent. In contrast, the baboons used in the head trauma research were perceived to be experiencing great suffering, as evidenced by the images on the videotape shot by the researchers themselves. In terms of potential benefits, there was a direct exchange of the baboon's life so that Baby Fae could live (no matter that the

attempt failed) while the head trauma research promised only some vaguely identified possible benefit sometime in the future (Rowan, Loew, and Weer, 1995).

The public's view of laboratory animal treatment and standards has changed considerably since 1948 when a Gallup poll found that four-fifths of the public supported the use of dogs in medical research and thought they were well cared for. There is a certain irony in this since, in 1948, there were no laws and governmental regulations addressing laboratory animal treatment. Today, the laws and regulations governing the use of animals in research require significant attention (not always carried through as fully as The HSUS considers necessary) to minimizing animal pain and distress yet the public is much more equivocal about such animal use.

IV. Legislative Mandate

Early in the 1960s, legislation was introduced into the U.S. Congress to regulate animal research. However, it was not until 1966 and a Life Magazine expose of the deplorable conditions in the compound of a dog dealer that the U.S. Congress took action and passed the Laboratory Animal Welfare Act (Wayman, 1966). This original legislation regulated only the acquisition and handling of animals by dealers. It was amended in 1970 (and the name changed to the Animal Welfare Act, or the AWA) to include the care of warm-blooded research animals in research institutions (however, birds and lab-bred rats and mice, who account for 90% or more of all laboratory animals, were excluded from regulatory oversight by order of the Secretary of Agriculture). The species that are covered by the AWA regulations include non-human primates, dogs, cats, rabbits, guinea pigs, hamsters, farm animals (when used in biomedical research), and miscellaneous other mammalian species.

Two public scandals involving animal research in 1981 and 1984 led to a public clamor for more regulation, and two bills were passed by the U.S. Congress in 1985 that amended the AWA and that addressed Public Health Service policies on animal research. The text of the amended AWA and the associated regulations can be found on the Internet at www.aphis.usda.gov/ac/awainfo.html. The law applies to any use of mammals and birds in biomedical research, testing, and (post-secondary) education, regardless of which government agency or private institution is funding the project. Research facilities are not obligated to apply the AWA law or regulations to non -regulated species, nor report statistics on the numbers of mice, rats and birds experiencing various levels of adverse effects. USDA Policy 11 (see Appendix 1 or go to www.aphis.usda.gov/ac/polmanpdf.html) provides guidance on reporting and addressing animal pain and distress.

The second bill required the NIH to upgrade its requirements for animal research oversight. This bill, the Health Research Extension Act (HREA), mostly addressed Congressional reauthorization of the NIH, but one section contains animal welfare provisions governing research. These provisions were implemented through revisions in the Public Health Service (PHS) Policy on the Humane Care and Use of Laboratory Animals. The Policy deals largely with administrative procedures, such as setting up an

Institutional Animal Care and Use Committee (IACUC). The Policy calls upon research facilities to follow the provisions in the Institute for Laboratory Animal Resources (ILAR) Guide for the Care and Use of Laboratory Animals. The ILAR Guide was originally drafted (and periodically revised) for the NIH, so it is also known as the NIH Guide. (Internet links to the full text of the Guide, the Policy, and the HREA can be found at http://grants.nih.gov/grants/documentindex.htm).

The PHS Policy covers all vertebrate species, including rats, mice and birds, and therefore fills some of the gaps in AWA oversight. However, the Policy applies only to research funded by the PHS/NIH. It does not cover research funded by other sources, nor does it typically apply to animals used in commercial testing nor for education. In practice, most academic institutions apply the basic principles of the AWA and the PHS policy to all of their vertebrate research, not bothering to make distinctions about species coverage or the applicability of differing sets of oversight rules. However, some institutions, because of the species used or their sources of research funding (e.g. a biotech company using only mice and rats), are not subject to the AWA or the PHS Policy at all, and are therefore completely unregulated.

A direct result of the 1985 amendments to the AWA and the changes in PHS policy that occurred at around the same time was the establishment of the system of IACUCs. These are modeled after the human research oversight committees, known as Institutional Review Boards or IRBs. IACUCs have been specifically charged with reducing the pain and distress that may be experienced by animals used in research as a major focus of their activities. IACUCs review protocols submitted by Principal Investigators (PIs), and evaluate the proposed standards of care provided to the animals used as subjects in the study. IACUCs are also required (by the USDA regulators who oversee the conduct of animal research) to ensure that investigators have searched for alternatives if the research is likely to cause animal pain and distress, even if anesthetics and analgesics are used to prevent any pain and distress (as mandated by Policy 12 - see http://www.aphis.usda.gov/ac/polmanpdf.html).

Investigators do not have to demonstrate that they have considered or looked for alternatives if the animal research project is placed in the non-painful category. The implicit message is that animal pain and distress is of greater public concern than animal death (usually via euthanasia). Despite this regulatory emphasis on alleviating pain and distress, the USDA has provided only relatively limited guidance for Policy 11 on the topic. Studies involving toxic chemicals or pathogenic organisms are not listed as examples of projects that might cause pain and distress. Also, the indications are that the use of Policy 11 guidelines in AWA oversight is limited at best.

V. The System of Reporting Research Animal Pain and Distress in the U.S.

Each research facility using regulated animals is required to report annually to the USDA the way its animals were used in research, with the numbers of animals placed in different 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 each category 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 for each category in Policy 11 is slightly different and is as follows (modified to use same form 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.

The actual wording on the Annual Report form provides an interesting legalistic loophole which is being exploited by at least one research institution. A careful reading of Columns 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. Tulane University, the institution in question, has argued that it has a policy of not approving any research project in which drugs could not be used to alleviate pain and distress. Therefore, they argue, none of the animals in its research projects could be placed in category E. They imply that all animals receive appropriate treatment to alleviate significant pain and distress. We have queried this, especially in cases where infection with pathogenic organisms has caused the deaths of monkeys. We do not believe it is possible, even with the use of drugs (other than permanent general

anesthesia), to alleviate the distress associated with the animals progress towards death. Also, the published reports in the scientific literature do not indicate any such use of drugs to alleviate the distress due to the infectious disease.

None of the institutions in Louisiana have reported any animal use in category E since 1993, which is one of the reasons we first started looking closely at research papers coming out of Louisiana. We do not believe that, under current approaches, it would be possible to conduct a significant amount of research on regulated species without causing some pain and distress that is not alleviated by drugs. Nationwide, 9.1% of the 1.214 million regulated animals used in 1998 were classified in category E and, in 1997, 8.0% of 1.268 million animals. (About 35% are usually placed in Category D and 55% in Category C.) The question that remains unanswered is whether these percentages are accurate. According to the analysis below, The HSUS believes they are too low.

VI. Critique of the Current Reporting System of Animal Pain and Distress

The current USDA reporting scheme has been criticized on a number of grounds (e.g. OTA, 1986).

A. For the first twenty years, there were no explicit definitions for "pain" and "distress" and there is still not a definition for "distress", although the USDA is now working to produce one.

B. The current pain and distress categories are confusing and there is no category for procedures causing pain and distress that are partially, but not fully, alleviated by the administration of drugs. In addition, there is no specific guidance on how to complete the annual report forms. As a result, institutions interpret the forms in their own ways. Thus, one institution might report a protocol in which the animals receive anesthesia but experience some post-operative distress as a Category D procedure (the animals received drugs) whereas another might interpret the same procedure as Category E (the animals experienced distress).

C. 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 animal use.The NIH reports mouse and rat use voluntarily and, in 1997, these two species accounted for 97.4% of the 762,398 animals reported used.

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 turned in late. This problem has been addressed in recent years and the Annual Reports are now more complete and also more accurate.

4. An analysis of the annual statistics on animal use for any reporting year reveals enormous (and unexplained) variation from state to state in the reporting of animals used in painful procedures without the administration of pain-relieving drugs. Table 3 documents the variation among states in reporting column E use for 1996. 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.

For comparison, the following states reported zero animals or less than 1% of the animals in Column E from 1995-1998 (with total usage in parentheses): Alaska (300), Arizona (5,000), Hawaii (5,000), Kentucky (500), Louisiana (16,800), Maine (800), Mississippi (2,000), Nevada (3,000), Oklahoma (4,300), Oregon (4,700), Rhode Island (2,100), South Carolina (6,100), Tennessee (10,900), Utah (4,600), Vermont (1,100), Virginia (19,200), West Virginia (1,700), and Wyoming (300). It is possible but unlikely that these numbers accurately reflect the way that animals are used.

Table 3. USDA data from 1996 on Column E (unalleviated pain or distress) use for states using more than 20,000 regulated animals.

State	% of Animals in Column E	State	% of Animals in Column E
USA	11.2	Missouri	15.7
California	3.2	Nebraska	10.7
Delaware	9.3	New Jersey	4.5
Georgia	13.9	New York	7.9
Illinois	3.2	North Carolina	8.0
Indiana	1.7	Ohio	4.9
Iowa	63.7	Pennsylvania	14.4
Kansas	40.2	Texas	1.9
Maryland	6.5	Virginia	0.5
Massachusetts	3.1	Washington	32.2
Michigan	2.8	Wisconsin	4.5
Minnesota	28.9	Federal Agencies	5.8

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 56.2%. For 1994, 1995, 1996 and 1997 the numbers bounced around from 21.3% to 0% to 0% and then back up to 35.5%.

For these and other reasons, many commentators have hesitated to draw firm conclusions from the USDA figures (e.g., Orlans, 1993).

D. The determination of which category to place a scientific protocol is usually done by the principal investigator (PI) under oversight from the IACUC prior to the start of the research study. Some institutions do a post-hoc analysis to see if their categorization is correct but, based on comments at meetings on IACUC function, most do not. A retrospective assessment would provide much more reliable numbers for the annual reports, and call greater attention to the recognition of pain and distress as it is being experienced by the animals.

Although the USDA publishes only summary statistics on pain and distress, the agency gathers considerably more information about column E procedures. Facilities are required to submit not only information on the numbers of USDA-regulated species that fall into column E, but also are required to describe the procedures themselves and explain why pain- or distress-relieving drugs were withheld. The USDA does not disclose this additional information in its annual reports but it can be obtained through the Freedom of Information Act (FoIA).

According to an analysis by USDA Animal Care staff of the 1998 Category E reports, the majority of the animals placed in category E (about 75%) are animals used in studies to comply with mandated Federal testing requirements - particularly animal vaccine safety and potency (unpublished USDA Report: Use of Animals in Research: A Study of Animal Welfare Act 1998 Annual Report Forms, July 1999). Over 50% of all animals placed in Category E were used to comply with regulations promulgated under the Virus, Serum, Toxin Act (9 CFR) and administered by APHIS, the USDA division that also oversees the AWA. Of the remainder, about 6.5% were used in disease studies, 3.3% in antibody/serology projects, and 2.0% in pain studies. Approximately 80% of the animals subjected to painful and/or distressing procedures were used by industry, with the remaining numbers being split fairly evenly between government facilities and universities/medical centers. Similar patterns have been documented for column E data from 1992 (Stephens et al., 1998).

VII. Approaches by Other Countries to Reporting Pain and Distress

When compared to the percentage of classified painful experiments conducted in foreign countries, the United States' numbers for research that causes pain or distress are significantly lower (see Table 4).

Table 4. Comparison of reported pain and distress numbers for four countries

Country (Year)	Total Animal Use	% Experiencing Moderate to Severe Pain and/or Distress
Canada (1996)	1,758,416	28.8
The Netherlands (1994)	770, 888	46.0
Switzerland (1997)	492, 186	30.2
United States (1997)	1,267,828	8.0

In Great Britain, the only indication of pain control that is available is the recording of anesthesia use. In 1978, 3% of the 5.2 million procedures involved anesthesia for the whole procedure (they were terminal) and 14% involved anesthesia for only part of the procedure. In 1988, 19% of the 3.5 million procedures involved anesthesia for the whole procedure and 17% involved anesthesia for only part of the procedure. It is not clear why anesthesia use doubled from 1978 to 1988 although the 1986 Act that revised British controls over animal experimentation placed greater emphasis on the control of pain and distress (The Alternatives Report, 1990). In 1997, 35.9% of animal procedures used anesthesia for some or all of the experiment. By comparison, in the USA, about 35% of all animals are placed in Category D (use of drugs to alleviate pain and/or distress, including anesthesia)

The Netherlands has made a concerted attempt to classify its research animal use by pain category. The 1994 Annual Report on animal experimentation notes that 54% of the animals experienced minor discomfort, 26% were likely to experience moderate discomfort and 20% were likely to experience severe discomfort. About one fifth of the animals in this last category were given medication to alleviate pain but they were still considered to be in discomfort (discomfort and distress is not always alleviated by analgesics). Examples of procedures that would place animals in the "severe" category are prolonged deprivation of food or water, some experimental infections, tumor induction, LD50 testing and immunization in the foot pad with complete Freund's adjuvant (The Alternatives Report, 1992).

The Canadians provide information on the use of anesthesia by different categories of research (see Table 5). The percentages can be compared with the fifty largest (in terms of NIH funding received) non-profit research institutions in the United States. The Canadians report that 13.25% of the animals used in basic research experienced moderate to severe pain. By contrast, the US research institutions reported a total of only 0.6% of animals used in 1996 and 0.8% of animals used in 1997 experiencing pain and distress (see Appendix II). In 1997, the NIH Annual Report identified only 0.7% of 23,958 regulated animals in Category E. We do not believe that the differences between Canada and the United States are real and suggest that this represents more evidence of significant under-reporting of animal pain and distress.

Table 5. Canadian Pain Classification Statistics 1996 (x 1000)

Pain and distress -Grade	Total	Basic Research	Applied Research	Safety Testing	Drug Development	Education
B (none)	542	333	52	70	29	58
C (Min)	709	537	95	56	11	11
D (Mod/Sev)	414	120	116	147	29	2
E (Severe)	93	13	5.5	74	0	0.3%
TOTAL	1,758	1,003	268	348	69	71
% D	23.6%	12.0%	43.3%	42.3%	42.3%	3.4%
% E	5.3%	1.3%	2.0%	21.4%	0.0%	0.4%
% D + E	28.9%	13.3%	45.3%	63.7%	42.3%	3.8%

Source: 1996 CCAC Animal Use Survey

It could be argued that the Canadian statistics include research done on mice, rats, birds and fish and that these animals are likely to experience much more pain and distress than the species regulated by the USDA. The Swiss have broken out the data on pain and distress by species (see Table 6). A similar classification of the US data is presented in Table 7. It does not appear as though the patterns of pain categorization for the different species are sufficiently large to account for the large differences in the percentage of animals reported to be experiencing pain and distress between the United States and the other countries.

Table 6. Swiss Pain Classification Statistics 1997

Pain / Distress Grade	None - Minor	Moderate	Severe	% Severe	% Moderate + Severe
Mice	190.847	67,689	22,913	8.1	32.3
Rats	101.013	35, 199	8,617	5.9	30.3
Guinea Pigs	10,610	3,471	1,610	10.3	32.4
Dogs	1,383	20	9	0.6	14.4
Pigs	2,116	190	23	1.0	9.1
Primates	334	77	28	6.4	31.4
Rabbits	4,660	1,455	72	1.2	24.7
TOTAL	343,3885	112,351	36,450	7.4	30.2

Source: Statistik 1997; Tierversuche in der Schweiz; Bundesamt fur Veterinarwesen (Department of Veterinary Affairs); 3003 Liebefeld, Bern

Table 7. United States Pain Classification Statistics 1997

	Total	E	% E
Dogs	75,429	1,671	2.2
Cats	26,091	378	1.45
Primates	56,381	840	1.49
Guinea Pigs	272,797	37,799	13.86
Hamsters	217,079	46,238	21.30
Rabbits	309,322	9,866	3.12
Sheep	33,048	72	0.22
Pigs	73,995	1,658	2.24
Other	203,686	2,638	1.30
TOTAL	1,267,828	101,160	7.98

Source: 1997 USDA Animal Welfare Report

VIII. Types of Research Causing Pain and Distress

Pain and distress caused by specific research models and techniques raise serious concerns for those in the animal welfare community as well as in the scientific community. For example, an animal's pain and/or distress is almost certain to affect experimental results in ways that are not necessarily predictable. The control groups are unlikely to experience the same degree of discomfort and distress as the experimental animals. Therefore, discomfort and distress have the potential to skew research results. Good estimates of how much animal pain and/or animal distress is caused by particular techniques or methods (with empirical evidence to support the estimates) are not yet available. For this very reason, gathering data to discriminate amongst research models and specific techniques is essential. Additionally, pain and distress may be specific to a particular research model, species, or gender and may affect the extent of suffering caused in that particular animal model (e.g., tumor site and burden).

According to the USDA statistics, animal use is split almost evenly between commercial and non-commercial users (Welsh, 1991; Newman, 1989) although these analyses leave out the federal laboratories which account for somewhere between 15-20% of national laboratory animal use. It seems as though the ratio between commercial, non-commercial and government laboratories in the USA may be around 45:40:15. In Great Britain, commercial laboratories have accounted for around two-thirds of the animal use with educational institutions and government laboratories splitting the remainder (Rowan, et al., 1995).

Of the 73,822 animals reported in 1992 experiencing pain and distress in testing procedures, vaccine potency testing alone accounted for 55%. Guinea pigs and hamsters involved in Column E procedures accounted for the majority (95%) of the animals used in vaccine potency testing. The remaining animals were involved in the heterogeneous category of toxicity or safety tests. Unfortunately, Column E descriptions typically are

too brief and generalized to permit a more detailed analysis of the procedures involved (Stephens, et al., 1998).

Much attention has been focused on the use of animals in the testing of personal care and household products although such use probably accounts for much less than one percent of the national demand for laboratory animals. In Great Britain, the testing of personal care and household products accounted for less than 5,000 animal procedures in 1990, or around 0.15% of total animal use. Among commercial organizations, the vast majority of animal use is involved in the discovery, development and testing of new medicines and therapeutics.

Specific Techniques

A preliminary list of research models/research areas has been compiled (see Table 8) and divided into two categories depending on whether the ensuing distress is the result of pain or the result of fear, anxiety, discomfort, illness or some other adverse effect. There are overlaps, yet the distinction serves to draw attention to the relatively neglected issue of anxiety and fear in research animals.

Table 8. Areas of Research and Specific Techniques that Cause Pain-Induced and Non-Pain Induced Distress

SPECIFIC RESEARCH MODELS OR AREAS
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
Pain-Induced Distress
arthritis models
burn research
cancer research (tumor pain)

chronic pain studies (acute pain should not be a problem if IASP* guidelines followed)
inflammation studies
experimental surgery
muricide as a model of aggression, neophobia, etc.
orthopedic studies
trauma research
SPECIFIC TECHNIQUES
anesthesia after-effects
antibody production (polyclonal and monoclonal)
aversive stimuli (e.g. electric shock)
bleeding techniques (including retro-orbital bleeding)
Complete Freund's Adjuvant
control animals denied experimental treatments
deprivation limits (e.g., water, food, sleep or social partners/experiences)
dosing techniques (e.g., gavage)
granuloma techniques
gut loop studies
knock-out technology
surgery sequelae
CO2 anesthesia for rodents
IASP: Report of International Association for the Study of Pain; subcommittee on taxonomy.

IX. Recognition and Alleviation of Pain and Distress: Problems and Technical Issues

The HSUS recognizes that the systematic reduction of animal pain and distress in the research laboratory is obviously not a trivial task. First, there is much conceptual confusion in the use of such terms as pain, distress and suffering. Second, animal use in the laboratory and classroom is very varied. Nonetheless, while the techniques used in biomedical research are certainly numerous, it is certainly not beyond our scope to determine underlying principles of pain and distress in animals which can then be applied to the varied models and methods. Third, animal pain, distress and suffering are not easy to recognize or measure unambiguously and there is considerable opportunity for legitimate disagreement among scientists.

Terminology

Aversive or distressing stimuli can take a variety of forms. Some are physiological stressors (e.g. injury, surgery, disease, starvation and dehydration), some are psychological stressors (e.g. situations that induce fear, boredom, anxiety), and some are environmental stressors (e.g. restraint, excessive noise, the presence of people or other species and chemicals) and some are a mixture of stressors (ILAR, 1992). There are difficulties in assessing the severity of resulting adverse states. This, however, is a task that must be addressed.

The terms "pain", "distress", "anxiety", "fear" and "suffering" describe experiences, and responses to experiences that are, in most cases, unpleasant and hence undesirable. Such terms are commonly used in everyday language to describe both human and animal experiences. However, the difficulty lies in understanding exactly what is meant when we actually use such terms. Dictionary definitions are often circular and unhelpful. For example, in the 1967 unabridged Random House Dictionary, pain is defined as both a sensation of acute physical hurt or discomfort and as emotional suffering and distress. Suffering is then defined as undergoing pain or distress. The Random House and other dictionaries appear to view pain, distress, and suffering as synonyms. However, a closer analysis reveals that this assumption is not supported (see Table 9 for definitions of relevant terms.)

Table 9. Definitions of Pain and Distress Terms

NOCICEPTION- The process whereby potentially noxious and/or tissue damaging stimuli cause special receptors (nociceptors) to fire and send a nerve impulse along the nociceptive pathways. Pain perception may occur, but only when such nerve impulses are processed in the central nervous system. Pain perception is not a necessary part of nociception. *PAIN - An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage (IASP, 1979). Pain terms are very variable and people may talk of acute or chronic pain, or sharp or dull pain, for example. Pain is neither solely physical nor psychological, it is both.* *ANXIETY - An emotional state involving increased arousal and alertness prompted by an unknown danger that may be present in the immediate environment (Kitchen et al., 1987).Unlike pain, anxiety is a diffuse sensation that has no specific location in the body. Scientists who study anxiety have not developed a code of conduct to limit the extent of anxiety a non-human animal may experience and some assume that animals do not experience anxiety, although some effective anti-anxiety drugs have been discovered and studied in animal models.* *FEAR - An emotional state involving increased arousal and alertness prompted by an experienced or known danger present in the immediate environment (Kitchen et al., 1987).* *DISTRESS - A state in which the organism is unable to escape from acute stressors or adapt to an altered external or internal environment. In acute distress, the organism will try to escape but in chronic distress, the organism will commonly engage in maladaptive (e.g. learned helplessness) behaviors (cf. ILAR, 1992).* *SUFFERING - A highly unpleasant emotional response usually associated with pain and/or distress. (Kitchen et al., 1987). The adjective "emotional" stresses the affective nature of suffering. Suffering involves a threat to the "person-hood" or self-concept of an individual rather than simply to the organic body and is a metaphysical concept. It cannot be reduced to "operational" terms and is, thus, not easily incorporated into "objective" sciences.*

Most of the literature discussion about animal pain and suffering concentrates on pain, not suffering. A report from the Netherlands, entitled the "Definitions of Pain, Stress and Suffering and the Use of These Concepts in Legislation on Animal Suffering," has almost

no discussion of suffering itself although the term comes up frequently in the text (Voorzanger and de Cock Buning, 1988). The report on animal pain and distress by the Institute for Laboratory Animal Resources (ILAR, 1992) defines and discusses pain, distress, anxiety, fear and discomfort but deliberately excludes any discussion of animal suffering. For the ILAR working party, suffering could not be defined operationally and therefore could not be reliably assessed. Like the term "obscenity", people are confident they can recognize suffering when they see it, but they cannot define what it is. Pain is also a very complex and private phenomenon, but is nevertheless considered easier to measure and to ground in the empirical world of biomedical research.

In biomedical research, animals may experience pain, 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. In some experimental protocols, anesthesia or analgesics are thought likely to interfere with the results and are therefore not used, leaving the animal with persistent and unrelieved pain. There is both a an animal welfare and a scientific need to understand animal distress and fear, and their relationship to pain.

Assessing Pain

Typically, we resort to observations of non-verbal behavior, such as moaning and crying, writhing, wriggling and so on to infer the presence of pain perceptions in animals. Pain also has typical physiological and neurophysiological correlates which, unlike the phenomenological (or felt) occurrence that is pain, are subject to direct empirical investigation. For example, nociceptors (the nerve endings that, when stimulated, are associated with pain perceptions) have been found in all mammals and in other vertebrates. In addition, direct, percutaneous recordings in human subjects have demonstrated that feelings of pain are correlated with activity in the small myelinated (A-delta) and unmyelinated (C) nerves. Research on anesthetized mammals indicates that these same nerve fibers are activated exclusively (or most potently) by stimuli of noxious intensity. Such nerve fibers appear to be present in all vertebrates. Similarities between humans and animals have also been demonstrated in the central nervous system pathways involved in pain perception.

Thus, reasoning from analogy, from neuroanatomy, from neurophysiology, from neurochemistry, as well as from behavioral observations, most people conclude that animals, or at the very least the warm-blooded vertebrates, probably experience pain that is qualitatively and quantitatively similar to that experienced by humans. The USDA guidelines on pain in animals state that if one has reason to believe that a stimulus would be painful to humans, it should also be regarded as painful to animals.

Anxiety and Distress

Pain researchers have paid considerable attention to the use of limited levels of painful stimuli in animals. For example, the International Association for the Study of Pain (IASP) has set up guidelines in which researchers are urged to design only projects in which animals are given the opportunity to terminate any painful stimulus and thus control the level of pain they experience (IASP, 1979). Some of the simpler pain research protocols (e.g. the tail flick and hot plate tests) involve systems where the animals makes the choice to end the pain by moving themselves or their tail away from the stimulus. The tail flick and hot plate devices are also fitted with automatic cutoff switches so that, in the event the analgesia under study is very effective, the animal will still not suffer any tissue damage.

Similarly, one can develop systems that allow animals to "volunteer" for pain research by offering them a highly desired food or drink. Such animals are willing to accept some painful stimuli in order to gain the reward. However, at the pain tolerance threshold, they voluntarily choose not to participate any further. Primates appear to have very similar tolerance thresholds to humans. In all of the above cases, the research protocol allows the animal to control when the painful stimulus is terminated. There are some studies (e.g. of chronic pain) where such refinements are not possible but even here pain researchers have tried to ensure that the animals do not endure a significant level of pain (Casey and Dubner, 1989).

By contrast, researchers who study anxiety in animals, which is arguably just as, if not more distressing to animals, have not developed similar guidelines and approaches. Some may not have paid attention to animal anxiety because they do not believe that animals can be anxious although they can experience the more "primitive" emotion of fear (e.g. Cassano, 1983). It is not exactly clear what the difference might be between fear and anxiety. One might fear some definable danger whereas anxiety may refer to that state of uneasiness where the threat is undefined and elusive. However, there is at least one relatively clearly defined neural substrate that appears to be involved in mediating anxious states and this substrate was, interestingly, found to be present in all vertebrates but in none of the invertebrates examined. This substrate has come to be known as the benzodiazepine receptor because it binds the anxiolytic benzodiazepine drugs such as valium with high affinity. It also binds alcohol and the barbiturate drugs which diminish feelings of anxiety as well.

Building on investigations of drug binding to the benzodiazepine receptor and its subsequent behavioral effects, Gray (1982) has produced a comprehensive theory of anxiety in which he argues that "...'human anxiety', or something very like it, exists also in animals ...." Gray suggests that many people may find this conclusion hard to accept. This is because of the common belief that anxiety is an almost uniquely human state, dependent on such complex cognitive capacities as the ability to anticipate future events based on past experiences, to form a self image, or to imagine one's own mortality. Nevertheless, he argues that the observed effects of such anti-anxiety drugs as alcohol, the barbiturates, and the benzodiazepines in animals are so similar to the observed effects

of these same drugs in humans that it seems more parsimonious to argue that these agents act upon a state in animals that is similar to the human state of anxiety.

Research has also identified anxiety-causing compounds that bind to the benzodiazepine receptor in the central nervous system. The best known of these are the beta-carbolines which, when administered to humans cause intense inner strain and excitation, increased blood pressure and pulse, restlessness, increased stress hormone levels in the blood and stereotyped rocking motions. One human volunteer experienced such severe anxiety that he had to be physically restrained and injected with a benzodiazepine which provided relief within five minutes (Dorow et al, 1983). The administration of beta-carbolines to primates caused piloerection, struggling in the restraint chair, increased blood pressure and pulse, increased stress hormone levels in the blood and increased vocalization and urination (Ninan et al., 1983).

The similar reactions of human volunteers and primates to the beta-carbolines does not prove that both humans and primates experience the same sort of anxiety but it is hard to argue that animal "anxiety" is not a significant cause of animal distress and suffering. Gray (1982) has suggested that "anxiety" may have evolved from a biological behavioral system - the 'behavioral inhibition system' (BIS). BIS may confer an evolutionary advantage by stimulating a state of alertness to novel stimuli in an animal's environment, making the animal less likely to rush into danger. Excessive stimulation of the BIS can clearly cause animal distress and suffering, as exemplified by a strain of "nervous" pointer dogs (Reese, 1979). The distress (immobility, urination and defecation) in the nervous pointers caused by the presence of humans could be easily eliminated by appropriate drug therapy, suggesting that the problem might have been due to mutations in the pathways controlling the "anxiety/fear" response.

While the distribution of the benzodiazepine receptor in vertebrates appears to provide a relatively "clean" distinction between "sentient" vertebrates and "non-sentient" invertebrates, research over the past decade has produced a host of confounding factors. First, there are other benzodiazepine binding sites which have now been shown to be present in invertebrates (Lummis, 1990). These "receptors" are found in non-nervous tissue and they are different from those found in the central nervous system of vertebrates. Second, a variety of other receptors that mediate anxiety and other anxiolytic drugs have been identified. For example, cholecystokinin peptides and their receptors appear to be involved in mediating anxiety and panic (Derrien et al., 1994). Handley and McBlane (1993) describe a number of drugs including the increasingly popular anxiolytic, buspirone, that act through 5HT(serotonin)-receptors to mediate "anxiety" in both humans and animals. Thus, anxiety cannot be attributed to a single neurochemical system in the central nervous system. Nevertheless, it is abundantly clear from the pharmacology of anxiety in both animals and humans that anxiety can be a significant cause of distress and suffering in animals.

Distress and Suffering

Distress is functionally and physiologically distinct from pain, although the two may

often interact on a cognitive-emotional level. Distress involves the activation of neural pathways in the limbic system of the brain that process emotional response to pain, fear and anxiety. Distress itself is used as a qualifying, catch-all term for multiple negative states which precludes the opportunity to quantify this subjective state of being. In humans, verbal answers to specific questions can, in most circumstances, be provided but the human subject may still be concealing his/her internal states (hence the uncertainty of lie detector tests). Animals are non-verbal and cannot similarly express and describe their feelings. Consequently, distress may be measured only by external standards. Given this limitation, and the relatively small degree of attention given to understanding the welfare implications of stress in animals, there are currently few methods that are applied in identifying and reducing the distress caused to animals in research.

Pain, fear, anxiety, discomfort and distress are all negative subjective states of being, and are typically described and grouped together under one larger heading of "suffering". "Suffering" is a widely used and abused colloquial term that has been subjected to very little careful analysis, even in the case of human suffering. Cassell (1982), one of the few to address the biological and psychological roots of human suffering, argues that suffering occurs when the integrity of a person (not the body) is perceived to be compromised or threatened in some way. (Person-hood is defined in terms of an individual's mental life and is distinguished from the organic body). Damage to organic tissues can and often does lead to suffering but, for Cassell, it is the psychological reaction to such damage that is the key to understanding the idea of suffering.
The notion that suffering arises from a perceived threat to the integrity of a "person" has significant ramifications for any discussion of animal suffering. Animals would, according to the above definition, suffer only if they possess to some degree the qualities of person-hood. In a later analysis, in which he specifically addresses the issue of animal suffering, Cassell (1989) (and more recently Byrne, 1999) argues that only beings with a sense of the future (anticipation) and a sense of self are capable of experiencing suffering. Some animals do appear to have a sense of self (e.g. chimpanzees and other great apes) and a sense of the future or, at least, seem to be able to anticipate and reflect on future events. How far such abilities extend through the animal kingdom would necessitate a much more detailed analysis than is possible here. One could also argue that only animals that are capable of affective (e.g. emotional) responses might be included among the category of beings capable of suffering (Damasio, 1994).

It is quite clear that few, if any, people use suffering in the narrower sense articulated above - referring only to perceived threats to the "person" rather than simple vigilance to protect against threats to the non-reflective organism. Even scientists who object to using the term "suffering" when referring to animal distress will, nevertheless, still argue vehemently that animals (including invertebrates) are capable of suffering. However, the colloquial term "suffering" has such broad meaning that it cannot be used profitably (even after careful definition) when trying to assess the severity of aversive stimuli to animals, or even to discuss the level of distress experienced by animals.

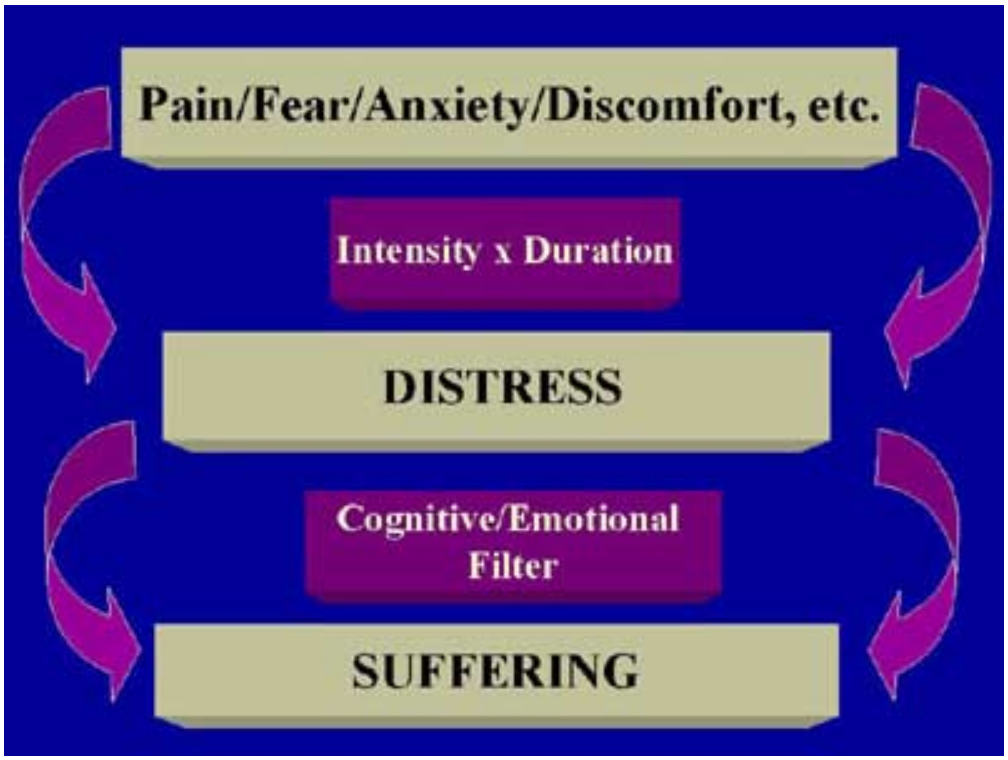
The Relationship Between Pain, Fear, Anxiety, Distress and Suffering

In order to understand the underlying reasons for animal suffering and to alleviate its occurrence in laboratory animals, we must first examine its components. In the model presented in Figure 1, pain, fear, anxiety and discomfort are all aspects of the external, behavioral manifestation of underlying processes. For instance, a painful stimulus applied during an experimental procedure, given its intensity, duration and frequency of application, may lead to anxiety and fear. The animal comes to expect (predict) the arrival of the painful stimuli and therefore develops anxious and fearful reactions to any prior stimuli that are linked in time and space to the onset of pain. The sight of the hypodermic needle approaching, causing an animal to cringe, is one example. This cascade of cognitive-emotional responses can be termed 'distress'.

The cognitive-emotional filter through which an animal perceives its subjective experiences of the external world will in turn influence its internal states of being. If the animal perceives that the onset of pain is to be expected, perhaps on a daily or hourly schedule, it may suffer emotionally from the anticipation or expectation of the pain. In this case, the animal's emotional state and behavioral response may extend beyond its initial responses to the degree of pain inflicted by the original stimuli. Thus, the negative emotional states experienced by the animal may not only contribute to but increase its sensitivity to the painful stimuli it anticipates.

The well-studied state of "learned helplessness", which occurs in both human and non-human animals, illustrates the point that cognitive-emotional suffering may be even more intolerable to an animal than the physical infliction of pain. Animals in states of severe suffering may display learned helplessness in which they typically show no response or attempts to withdraw or protect themselves from mildly painful or harmful stimuli. Humans who display learned helplessness are typically individuals who have been subjected to various forms of physical and mental or emotional abuse. This gives an idea of the perceived events that an animal has experienced to reach the stated of learned helplessness.

Figure 1. Model of Pain, Distress, Anxiety, and Suffering



To lessen the potential slide downward of captive animals' behavioral and mental/emotional states into boredom, frustration, depression and finally severe apathy (learned helplessness), it is necessary to provide both social and physical environmental enrichment (see Wemelsfelder,1999, for a discussion of this topic). Some aspects of enrichment involve rewarding and reinforcing social, physical, and other environmental stimuli. Promoting well being, however is not quite as simple as providing a "likable" experience. If an animal is provided with food and water in a safe environment, why do we not consider this necessarily sufficient to maintain a state of well-being (see Shepherdson, 1999, for a discussion of this issue)? Experiments indicate that captive animals will preferentially work for food rather than eat what is freely available, indicating that foraging activity is itself rewarding (contra freeloading: see Young, 1999). Play behavior is certainly associated in humans with well being and pleasure, but how would we increase the incidence of such behavior in captive animals? In fact, while we may think we know play when we see it, behavioral scientists argue endlessly over how to define animal play and what such behavior might mean (see Mitchell, 1990).

Anthropologists and sociologists recognize that certain tasks carried out by human beings involve psychic costs to those human beings. Working in an animal slaughter plant would be very unpleasant for most people. In some cultures, slaughter is conducted by people of particular spiritual development and strength (e.g. the schochet in kosher slaughter) that permits them to bear the burden of taking the life of a sentient creature. Hunter/gatherer societies have rituals that help the hunters cope with the burden or guilt of killing an

animal. Similarly, the taking of an animal's life in a research project or the infliction of pain and suffering on laboratory animals causes burdens that must either be continuously confronted or repackaged in certain customs and habits (e.g. the "sacrifice" of "numbered" and un-named animals) in order to make the burdens more bearable (Arluke, 1988 & 1989). Such laboratory conventions and customs allow caring people to do the research despite the harm caused to the millions of sentient animals used every year. (Lest those of us who are not involved in animal research become too smug, it should be noted that eight billion animals are raised and slaughtered in the United States each year, under living conditions that range from poor to horrendous, to satisfy the demands of 90% or more of the public for hamburgers, spare ribs and chicken wings.)

The problem with the development of "distancing mechanisms" is that distance can lead to people ignoring or overlooking costs that, with more attention, could be alleviated or avoided altogether. Human neonatal surgery is a classic example of the danger of such distancing mechanisms. While most humans can report whether or not they feel pain, animals cannot and this has led to problems in acknowledging animal pain (see Beynen et al., 1987 and Phillips, 1994 for examples). Non-verbal human infants were, until recently, also denied the capacity to fully experience pain, confirming the importance of verbal report in legitimating pain perception (Anand et al., 1987). According to Daniel Tibboel (Personal communication - November, 1998, Zeist), in 1987 it was found that 85% of neonatal anesthesiologists agreed that human infants could experience pain but only 5% actually delivered pain relief. By 1996, 85% were giving pain relief. Thus, drawing attention to the issue of infant pain had a dramatic effect on the delivery of pain relief. It is also possible to study pain perception in animals using the same sort of techniques and reasoning by analogy as in human infants.

The fact that human neonates 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 not insignificant amount of the pain and distress of non-verbal laboratory animals is overlooked and/or its severity discounted. There is only one research study that looked specifically at this issue (Phillips, 1994) and it confirmed the suspicion that animal pain and distress are not addressed as vigorously as they should be.

X. HSUS Pain & Distress Initiative

For the most part, our ability to detect pain, and more importantly, distress, in laboratory animals is very limited. We lack good measures and methods for quantifying distress in the common laboratory animal species. To address this lack of knowledge and our inability to generate objective measures of negative subjective states, and to promote laboratory animal welfare, The HSUS has launched a campaign to eliminate pain and distress in laboratory animals by the year 2020. It is apparent that those who use and care for laboratory animals are already concerned about animal pain and distress. In conjunction with IACUCs, they have played a significant role in addressing problems of animal pain and distress in the past ten to fifteen years. Nevertheless, The HSUS believes that a more systematic approach will hasten achievement of the campaign goal.

The HSUS Pain & Distress Initiative consists of the following four components:

1. Development of a detailed, referenced technical report on animal pain and distress: The HSUS has convened an international group of experts including laboratory animal veterinarians, animal behaviorists, physiologists, neurologists, veterinary anesthesiologists, philosophers and others to develop and author a comprehensive report on the subject. The group is chaired by Dr Joy Mench of the University of California, Davis and the report is due to be completed this year. The group is having particular difficulty in developing guidelines to address the likely distress that specific research techniques might cause since the empirical data is buried in the literature and not easy to find.

2. The topics that this pain and distress working group will cover in the technical report are:

- Definitions of animal pain, distress, discomfort, anxiety, fear and suffering
- The biology of pain and distress
- Recognition of animal pain and distress: current and potential approaches
- Alleviation of animal pain and distress
- Housing issues
- Pain and distress caused by specific techniques and research endpoints
- Conclusion and recommendations
- Appendices

3. Outreach to Institutional Animal Care and Use Committees (IACUCs):
The HSUS is reaching out to seek the co-operation 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. Specifically, The HSUS has invited IACUCs, which already have a statutory mandate to minimize pain and distress, to join in the Initiative.

The HSUS has begun facilitating an exchange of information and policies among IACUCs so that new ideas and initiatives, including "best practices" and humane endpoints (ILAR, 2000), can be disseminated quickly. We have sent five mailings to the chairs of the over 1800 IACUCs nationwide through March, 2000. The mailings are primarily informational in nature, alerting IACUC chairs to upcoming meetings and new publications, as well as informing them about the Pain and Distress Initiative. Feedback from IACUC chairs has been minimal, but responses from a survey in one of the mailings indicated that over 90% of the (few) respondents found the mailings helpful and wanted to continue receiving them.

As part of our efforts to raise the profile of pain and distress issues with IACUCs, The HSUS will focus on specific research areas, practices, and techniques where relatively little attention has been given to animal suffering. Our aim is to seek out new approaches to recognizing, measuring, and alleviating animal distress. We have commissioned the development of a report on weight loss as an index of

animal pain or distress and have also begun to research whether CO2, a widely used agent for the anesthesia and euthanasia of rats and mice, is aversive and causes significant distress to the animals.

4. Regulatory Aspects

The HSUS supports a proposal to alter pain and distress reporting under the Animal Welfare Act that would discriminate between the following levels:

- no/little pain/distress,
- moderate pain/distress, and
- severe pain/distress.

While waiting for the possible implementation of a new reporting scheme, The HSUS seeks to develop some consistency in how pain and distress are currently reported (see Section XI).

We will encourage the development and issuing of "best practice" guidelines covering specific techniques and research areas so that the many different IACUCs have some base line guidance for their own decision-making. An example of such an initiative is the letter sent out by the Office for the Protection from Research Risks at NIH (now renamed as the Office for Laboratory Animal Welfare) stating that ascites antibody production in rodents causes distress and should be used only if in vitro production of monoclonal antibodies is unsuccessful.

5. Financial Support for Research on pain and distress

One of the problems in the field of pain or distress measurement and elimination is that there is virtually no funding to support relevant studies. Clearly there are difficulties in encouraging agencies to provide funds for projects that might deliberately cause animal distress. However, it should be possible to "piggy-back" such assessments onto ongoing studies that are investigating other topics that have already been approved. The HSUS plans to lobby both private and government entities to make available funds that might be used to develop more sensitive and accurate measures of animal distress that are practical in the laboratory and ways in which such distress can be alleviated.

Best Practices and Policies

Many institutions and animal facilities have developed policies and guidelines in which the pain and distress caused to animals are minimized or alleviated entirely. These documents are usually only available in-house (although the world-wide web is making some inroads in this regard since more and more internal policy documents can be accessed by people outside the institution) and are not disseminated to other institutions and laboratories through professional publications. The HSUS plans to promote the dissemination of best practices by encouraging institutions to publicize their efforts on reducing pain and distress in animals used in research.

An analysis of some of the policies covering specific techniques indicates that there is considerable variation in what is permitted from one institution to another. The HSUS has summarized some of the policies on specific techniques and is distributing some of these analyses to the IACUCs via our periodic mailings. We have begun the process with an analysis of policies on the production of monoclonal antibodies gathered from the World Wide Web (see Table 10). The question is, which one of these policies causes less pain and distress to the animals, and what can be considered to be a 'best practice'? It is clear that more inter-institutional discussion and empirical studies are needed to assist scientists in making a determination on this and other policies.

Table 10. Analysis of Policies on the Production of Monoclonal Antibodies

	Penn State	Stanford	U Iowa	U Minnesota
Monitoring subj. w/ solid tumors	Not specified	3/ wk	Not specified	3/ wk
Priming	as low as 0.1 ml pristane	Not specified	0.2 ml max pristane	0.5 ml max pristane
# of taps	max 3 taps, last terminal	Not specified	2 taps, last after euthanasia	Not specified
Monitoring post inoculation	daily	3/ wk for 1st wk, then daily	daily	daily
Replacement fluid after ascite harvest	Not specified	1-2 ml of saline subcutaneous	Not specified	Not specified
Anesthesia during tap	anesthesia can be used	anesthesia used for new personnel	Not specified	Not specified

**** Institutional Animal Care and Use Committee policies on the production of monoclonal antibodies were retrieved from the World Wide Web. Policies were reviewed and organized into a table for the purpose of comparing similarities and differences among institutions. The table depicts a variety of policies for monoclonal antibody production.***

XI. Recommendations and Proposals

The current USDA pain categories (Table 11) have been widely criticized by scientists and animal protectionists alike (see Section V of the White Paper). Table 12 presents a proposal for a modified system that is a true pain scale similar to those used in other countries, such as The Netherlands and Switzerland. This scale has been developed and approved by an eight member committee consisting of animal research and animal protection organizations. The USDA has yet to take action on the proposal.

Table 11. Current USDA Reporting Scheme

USDA Category	Pain and/orDistress	Anesthesia/Analgesia	Full IACUCReview	Alternatives Literature Search
C	Minor or None	No	Maybe	No
D	Yes or No[1]	Yes	Yes	Yes
E	Yes	No	Yes	Yes

[1] Animals listed in column D were given pain- or distress-relieving drugs, but these drugs may not have been sufficient to relieve all pain and distress throughout the experiment. The USDA could implement the new system so that protocols with little or no pain or distress (including those where pain and distress are completely alleviated by anesthesia and analgesia) could be exempt from alternatives literature searches and full IACUC review.

Table 12. The Proposed Reporting Scheme

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

Until a new pain classification system is implemented, there are a number of ways that the USDA could improve the current system, such as:

- increasing facility compliance and oversight of the "requirements" to provide descriptions of Column E procedures and explanations for withholding pain and distress relief
- increasing the level of detail in Column E descriptions to enable reviewers to create a more detailed classification of experimental procedures
- creating a mandate for facilities to provide year end totals and summaries of all protocols using animals in Column E for examination by USDA inspectors
- providing IACUCs with clear definitions and examples of levels of suffering, pain, distress, stress, and anxiety
- clearly defining when animals and studies must be classified into Column E

- clarifying what "pain" and "distress" (especially distress) mean for different species under different circumstances
- providing IACUCs with clear instructions on how to complete the Annual Facility Reports
- expanding the reporting system to include all species that the USDA has legislative authority to regulate (mammals and birds), particularly laboratory-bred mice and rats
- closely monitoring research facilities' classification and reporting of animals

In addition to recommendations concerning the reporting system, The HSUS makes the following recommendations related to alleviating pain and distress:

- Journals should adopt a policy of requiring manuscript authors to provide full details on the use of pain- and distress-relieving drugs and other treatment interventions
- The HSUS challenges peer-reviewed scientific journals to adopt a "no death as an endpoint" policy in order to further progress the implementation of humane endpoints into research
- Funding institutions should provide support for refinement research
- The NIH should issue "best practice" and "humane endpoint" guidelines to facilitate the pace of innovation in laboratory animal welfare

XII. Summary and Conclusions

The public's support for animal use in biomedical research has declined in recent years. The decrease in support is even more evident when the public is questioned about the experimental use of animals involving pain and/or distress. In this instance, the level of public support decreases significantly when harmful research is conducted on primates, dogs and cats (Plous, 1998). With the public's interest in the humane treatment of animals in laboratories and research, there should be greater attention provided to refining techniques, to publicizing best practices, and to eliminating animal pain and distress. The HSUS Initiative seeks to encourage methods of refinement and replacement, with the goal to eliminate all animal pain and distress in research by the year 2020.

What does the research and speculation about animal pain, suffering and anxiety tell us about animal well being? First, it is clear that we have to broaden our concerns about pain to include a number of other states, such as anxiety and fear that are capable of producing considerable suffering. Second, as suffering is conceived in the discussion in this paper, it appears as though it may not be distributed as widely through the animal kingdom as our vernacular use of the term might suggest. Damasio (1994), for example, argues that suffering arose in creatures that possess sophisticated neurophysiology/neuroanatomy capable of large-scale storage (memory) of a multitude of categories for objects and events. These memory capabilities are then available for manipulation and creation of novel solutions.

In the promotion of well being we have some responsibility not simply to minimize animal pain, distress and suffering but also to enrich and enhance the existence of

animals that we use and keep for human benefit. This is what may lie behind efforts to develop environmental enrichment programs for zoo and laboratory animals, and the pressure to change minimum standards of animal care into optimal standards. However, if our understanding of animal pain, distress and suffering is confused and incomplete, our knowledge of what might constitute animal well-being is even more insubstantial.
The HSUS commends the USDA for initiating its own analysis of pain and distress reporting, and developing a proposed set of solutions for reducing animal pain and distress in a recent report (unpublished USDA Report: Use of Animals in Research: A Study of Animal Welfare Act 1998 Annual Report Forms). The thorough nature of the analysis and its concomitant recommendations will help further attention to animal pain and distress issues, and hasten the progress of its alleviation.

In the past few years, fortunately, there has been an increase in attention to pain and distress issues within science and academe. The result is steady progress in the form of experimental data addressing animal distress and well being and an increase in the debate about the conceptual issues. These activities will lead to improvements for both animals and the humans that rely on them. In the end, better animal welfare will lead to better science; unless the pain and distress, unwanted factors, are eliminated, they will always confound scientific data and ultimately translate into poorer human welfare as well.

XIII. References

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XIV. Appendixes

APPENDIX I: USDA Policy 11 on Pain and Distress
http://www.aphis.usda.gov/ac/polmanpdf.html

Policy #11 --- Painful/Distressful Procedures --- April 14, 1997

- References: AWA Sections 13(a)(3), 13(a)(7), 13(e)(2, 3) and 9 CFR, Part 2, Sections 2.31(d)(1)(i,ii,iii,iv), 2.31(e)(4), 2.33(b)(4) and 9 CFR, Part 3, Section 3.6(b)(5,6,7)
- History: Replaces letters dated May 8, 1992, November 7, 1991, November 9, 1990, and March 1, 1990.
- Justification: Provides requested guidance. Procedures involving animals will avoid or minimize discomfort, distress and/or pain.
- Policy: 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. The Institutional Animal Care and Use Committee (IACUC) is responsible for ensuring that investigators have appropriately considered alternatives to any procedures that may cause more than slight or momentary pain or distress. A written narrative description of the methods and sources used to search for alternatives must be provided. Where specific testing procedures are required by Federal law, the CFR references or other legal guidelines requiring them should be noted.
- Examples of procedures that can be expected to cause more than momentary or slight pain include, but are not limited to, the following:
    - Terminal Surgery is considered a painful procedure which is alleviated by anesthesia.
    - Freund's Complete Adjuvant used for antibody production may cause results ranging from momentary or slight pain to severe pain depending on the product, procedure, and species.
    - Ocular and Skin Irritancy Testing. The dosing procedure itself is generally not painful but the reaction caused by the product being tested may cause pain.

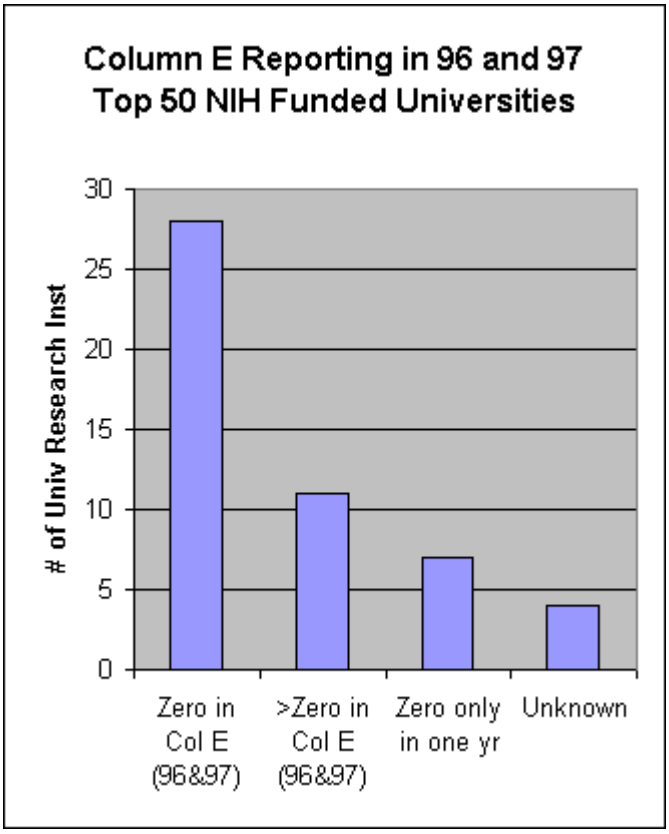
- Examples of procedures that may cause more than momentary or slight distress include, but are not limited to, the following:
    - Food or water deprivation beyond that necessary for normal presurgical preparation.
    - Noxious electrical shock that is not immediately escapable.
    - Paralysis or immobility in a conscious animal.
    - Many procedures, including any of those in the lists above, may cause both pain and distress. An example of a procedure that can be expected to cause more than momentary or slight pain as well as distress would be a study involving extensive irradiation.
    - Animals exhibiting signs of pain, discomfort, or distress such as decreased appetite/activity level, adverse reactions to touching inoculated areas, open

sores/necrotic skin lesions, abscesses, lameness, conjunctivitis, corneal edema, and photophobia are expected to receive appropriate relief unless written scientific justification is provided in the animal activity proposal and approved by the IACUC.

- Research facilities must have a mechanism in place for ensuring that animals are reported in the appropriate pain category on the annual report (APHIS Form 7023). Individual animals that do not experience pain/distress from testing procedures should be reported in column C. Individual animals experiencing pain/distress which is alleviated with anesthetics, analgesics, sedatives and/or tranquilizers should be reported in column D. This category includes terminal surgery under anesthesia. Individual animals in which needed anesthetics, analgesics, sedatives, and/or tranquilizers are withheld should be reported in column E. For all column E animals, a written justification, approved by the IACUC, must be provided, including CFR references or other guidelines if appropriate.

APPENDIX II. Top 50 NIH Funded Non-Profit Research Institutions Use of Animals and Category E Reporting*

Table Summary in Graph Format



**Although The HSUS believes there is significant under-reporting of pain and distress (especially distress) by US research institutions, we do not believe this under-reporting to be planned or intentional. We believe the lack of adequate data is due to:*

1. *The inherent difficulties of assessing animal pain and animal distress*
2. *The lack of attention to addressing these issues by regulators and the research community*
3. *The natural tendency to downplay the unpleasant consequences of actions taken to produce substantial social benefits (e.g. knowledge, improved health care).*