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## **Unrelieved Pain and Distress in Animals: An Analysis of USDA Data on Experimental Procedures**

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### CITATION

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### ABSTRACT

Pain and distress are core issues in the field of animal experimentation and in the controversy that surrounds it. We sought to add to the empirical base of the literature on pain and distress by examining government data on experimental procedures that caused unrelieved pain and distress (UPAD) in animals. Of the species regulated by the U.S. Department of Agriculture (USDA), most of the approximately 100,000 animals subjected to UPAD during the year analyzed (1992) were guinea pigs and hamsters. Most of these animals were used in industry laboratories for various testing procedures, primarily vaccine potency testing. We discuss the limitations of the USDA data and recommend changes to the current reporting system. By identifying experimental procedures that cause UPAD in large numbers of USDA-regulated animals, the present analysis can be viewed as a means of identifying priorities for research and development of alternative methods (replacements, reductions, and refinements).

Pain and distress figure prominently in the literature of applied animal welfare science and related disciplines. In the field of animal experimentation, pain and distress have been discussed from a variety of perspectives, such as how to define these aversive states, how to assess their distribution across the animal kingdom, how to recognize and alleviate their expression in different animal species, how to quantify their levels, and how to prevent or minimize their effects (U.S. National Research Council, 1992).

The U.S. National Research Council (NRC) characterizes pain as resulting "from potential or actual tissue damage. Pain can be considered a potent source of stress....It can also be considered a state of stress itself" (NRC, 1992, p. 5). The same report defines *distress* as "an aversive state in which an animal is unable to adapt completely to stressors and the resulting stress and shows maladaptive behaviors" (p. 4).

Pain and distress are not the only aversive states that animals in laboratories can experience; others include fear and anxiety. Death can be considered the ultimate aversive state or harm. Nonetheless, pain and distress are considered key components of the "costs" to animals from experimental procedures

(Orlans, 1993). Not surprisingly, pain and distress are important reference points in ethical analyses of animal research (Singer, 1975), in national legislation and regulations (Code of Federal Regulations, 1995), in public attitudes about animal research (Rowan, Loew, & Weer, 1995), and in public education materials defending or criticizing animal research (Diner, 1979).

In light of the public controversy over animal research, concerns have been raised by several sociological studies bearing on the issues of pain and distress, including the degree to which (a) research workers may fail to recognize or treat pain and distress (Phillips, 1993), (b) the prevailing attitudes among workers in a given laboratory may influence the handling and treatment of animals (Arluke & Sanders, 1996), and (c) published descriptions of experimental procedures may be "sanitized" to avoid provoking concerned lay readers (Lederer, 1992).

Despite the significance of pain and distress to issues surrounding animal research, U.S. statistics on these aversive states are limited. Various pain scales have been proposed, some are being used voluntarily by individual institutions (Orlans, 1993); however, none have been incorporated into public policy in the United States.

The U.S. Department of Agriculture (USDA) publishes annual statistics on pain and distress for species regulated under the Animal Welfare Act (AWA). The USDA's pain classification system has three categories. Their exact wording is somewhat confusing, but the USDA interprets them to represent the following situations (USDA, 1993):

- Procedures involving 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").

This scheme has been justifiably criticized on several grounds (Office of Technology Assessment [OTA], 1986). It has no category for procedures causing pain and distress that were partially, but not fully, alleviated with drugs. No definitions for the words *pain* and *distress* are provided. No guidance is provided on how to fill out the form.

Moreover, the USDA figures include only USDA-regulated species, namely, dogs, cats, rabbits, guinea pigs, hamsters, nonhuman primates, mammalian farm animals, and certain other mammals used in biomedical procedures (e.g., ferrets). The figures specifically exclude laboratory-reared mice and rats, which comprise an estimated 80-90% of the vertebrate animals used in U.S. laboratories (OTA, 1986), based on patterns in other countries where full records are kept (e.g., United Kingdom, The Netherlands). The USDA figures also exclude information on birds, reptiles, amphibians, and fish. For these and other reasons, many commentators have hesitated to draw firm conclusions from the USDA figures (Orlans, 1993).

Although the USDA publishes only summary statistics on pain and distress, the agency gathers considerably more information about column E procedures, which are those causing unrelieved pain and distress (UPAD). For these procedures, facilities are required to submit not only information on the numbers of USDA-regulated species that fall into column E, but also descriptions of the procedures themselves and explanations of why pain-relieving drugs were withheld.

Unfortunately, the USDA does not disclose this additional information in its annual reports. However, copies of the facilities' reports to the USDA are available to the public through the Freedom of Information Act (FOIA). The purpose of the present analysis was to explore the USDA's unreported data on UPAD, compiling--to the extent possible--a "demographic profile" of procedures that cause UPAD. Our aim was to make an empirical, descriptive contribution to the literature on pain and distress. We also sought to identify painful procedures carried out on large numbers of animals and thereby flag these procedures as potential priorities for research and development of alternatives methods (the Three Rs of replacement, reduction, and refinement).

## METHOD

We analyzed facility reports for the USDA's fiscal year (FY) 1992, the most recent year for which data were publicly accessible when our study began in June, 1994. These reports (USDA VAPHIS form 7023) were obtained from the USDA under the FOIA. We received copies of all annual reports filed with the USDA other than an unknown number filed after our request had been fulfilled.

In some cases, our totals differ from those compiled by the USDA in its FY92 *Animal Welfare Enforcement* report (USDA, 1993). The discrepancies may stem from several sources, including the USDA having had access to facility reports submitted late.

Some facilities voluntarily reported numbers of nonregulated species such as mice and rats. Given the sketchy nature of these numbers, we excluded them from our analysis.

We categorized the types of facilities where column E procedures were conducted. These categories were industry, university and medical center, and government. Industry facilities included contract testing laboratories, and pharmaceutical, industrial chemical, and medical products companies, as well as miscellaneous private companies. Government facilities included military laboratories, National Institutes of Health laboratories, and other federal and state facilities. Universities and medical centers included university (and college) facilities, medical centers affiliated with universities, and nonprofit research institutes.

We used the reported descriptions of column E procedures to classify these procedures according to their broad purpose. The descriptions tended to be brief ( 1-4 sentences) and general. Procedures were classified as either research, product development and safety testing (hereafter called testing), or education. Education included any use of animals for classroom exercises and demonstrations and for training in biomedical procedures. Testing was defined broadly to include any use of animals in assessing chemical or product efficacy, as well as in assessing chemical or product safety/toxicity. The following were the most common phrases that triggered a testing classification: *safety test*, *toxicity test*, *potency test*, *challenge test*, *drug screen*, *drug evaluation*, *pharmacologic* or *pharmacokinetic study*, *range finding study*, or *efficacy test*. Research included all other activities, whether basic (or fundamental) research or applied. Studies that mentioned modeling or antibody production were classified as research.

We subdivided the data in the research, testing, and education categories in cases for which we could identify common subcategories of procedures.

## RESULTS

We received and examined 1, 7 46 facility reports from FY92.<sup>1</sup> Of these, 248 (14%) reported using regulated animal species in column E procedures. Unfortunately, it was impossible to determine the total

number of column E procedures. Twenty eight facilities failed to provide any descriptions of these procedures. Many other facilities provided one general, conflated description for two or more procedures.

Table 1 provides a random sample of 10 procedure descriptions selected from facility reports. Note that two reports gave no descriptions (items 3 and 6), two failed to describe the actual procedures carried out on the animals (2 and 10), and one gave a one-word description that could refer to either an eye or a skin irritancy test (9).

According to our analysis, 102,384 animals of regulated species experienced UPAD during FY92. This figure differs substantially from what the USDA reported (120,208). The bulk of the discrepancy stems from the USDA's error of including 15,884 mice and rats (nonregulated species voluntarily reported) in its total.

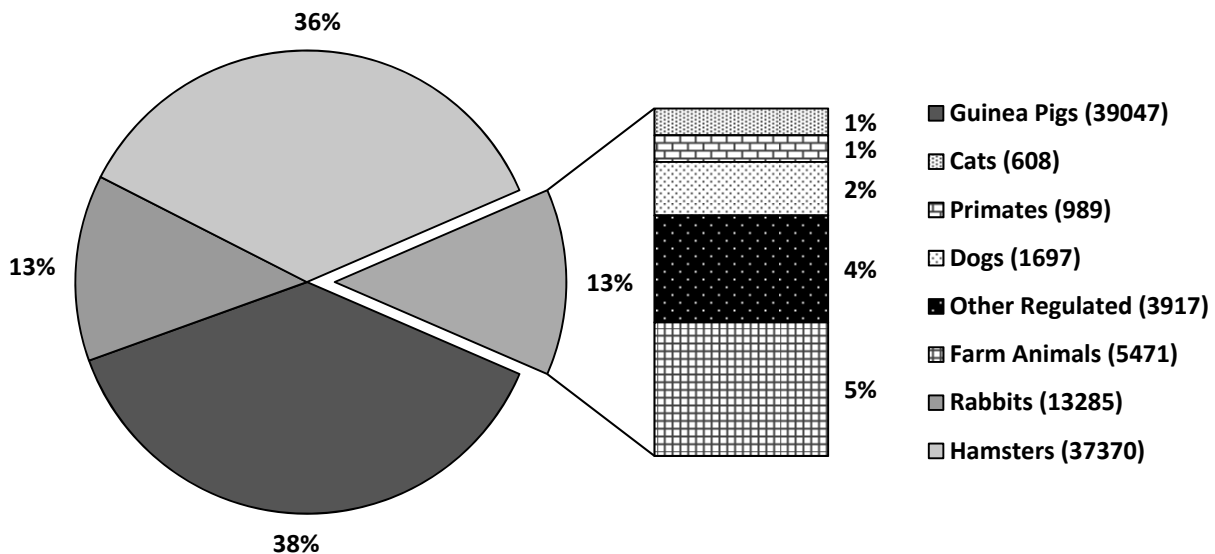
**TABLE 1**  
**Ten Randomly Selected Descriptions of Procedures Causing**  
**Unrelieved Pain and Distress in Animals**

*Note. Explanations of why pain-relieving drugs were withheld are not quoted here unless they shed light on the nature of the procedures carried out on the animals.*

1. "Three-hundred and three (303) guinea pigs were used for sensitization testing under the Topical Hazard Evaluation Program (THEP). The testing involved topical application of sensitizing agents followed by topical application of the challenge dose after a two week delay. This protocol entails the wrapping of the animals in an occlusive dressing for a twenty-four hour (24) period unrestrained; some distress at times may be associated with this procedure. This procedure (occlusion) is used to optimize skin penetration of the test compound. When an immune response is induced the host response scoring system may include, as evidence of the varying degree of response, both redness (erythema) and edema at the site of application."
2. "The animals we use in our projects [cattle] experience distress due to anaplasmosis."
3. [No description provided.]
4. "The 276 rabbits listed in Column E were used for dermal LD50 and ocular irritation studies. These studies were performed using the guidelines published in the Federal Register. The data generated by these studies is used to evaluate the toxicity or ocular irritation potential of novel compounds in development."
5. "Potency Test: Tuberculin Products. 25 Guinea Pigs. Due to the nature of the sensitizing material (killed Tubercle Bacilli, Jamaica 22 Strain resuspended in Drakeol, refined mineral oil) abscesses, which do not resolve, form at the site of injection. The previous method used to sensitize animals resulted in abscesses 100% of the time; while, the new method has reduced the level to -10% of the animals producing abscesses. The abscesses formed are sterile, and they do not impede movement. The potential problem occurs when the abscess ruptures. The time of rupture cannot be predicted for the use of tranquilizers, anesthetics or analgesics, and the wound caused by the ruptured abscess will heal as rapidly without treatment as with treatment."
6. [No description provided.]
7. "The 98 guinea pigs that experienced pain without benefit of analgesics or anesthetic during tests were used in skin sensitization tests required for the Federal Hazardous Substance Act regulation, the Federal Insecticide, Fungicide and Rodenticide Act regulation and the Toxic Substance Control Act regulation."

8. "Impairment of the normal immune response as a result of burns or other trauma often leads to septic complications and death from invading microorganisms. A highly reproducible model of shock-related immunosuppression as seen in trauma patients was developed [using dogs and guinea pigs]. This study addresses the time course of the effects of endotoxin on the immunocompromised patient and leads to a greater understanding of the effects on various components of the immune system including circulating factors and/or suppression of cell-mediated immunity. Initially a dose response study was done to determine a dosage with minimal undesirable effects. Following careful review by the IACUC, this study was approved with the condition that there be continual collaboration with the veterinary staff. Frequent observations were made in order to assure the earliest endpoint."
9. "Draize"
10. "The eight sheep enumerated under column "e" were listed under an approved Animal Care and Use Protocol specifying postoperative administration of butorphanol for analgesia. The principal investigator (PI) interpreted the protocol as reading that said analgesic was to be given only when in his judgment a subject exhibited signs of pain. The matter was referred to the Institutional Animal Care and Use Committee (IACUC). While the sheep, according to the PI display no outward manifestations of pain, following USDA regulations, procedures are presumed to be painful if similar procedures cause pain in man. IACUC, after careful deliberations, authorized the PI to complete three additional studies so as not to compromise data accumulated over a considerable period. Intercostal nerve resection, which would eliminate transmission of pain signals produced by thoracotomy, was proposed and approved by IACUC as an alternative to analgesics. However, IACUC decided to reopen the discussion on this protocol. The committee determined that intercostal nerve resection would not alleviate visceral pain associated with the procedure and required that to continue without analgesics, the PI must provide scientific proof showing butorphanol (0.2mg/kg body weight) would interfere with lymph flow, the reason given for precluding their use."

**FIGURE 1** Number of animals of various USDA-regulated species who experienced unrelieved pain and distress (column E procedures) during 1992. N = 102,384.



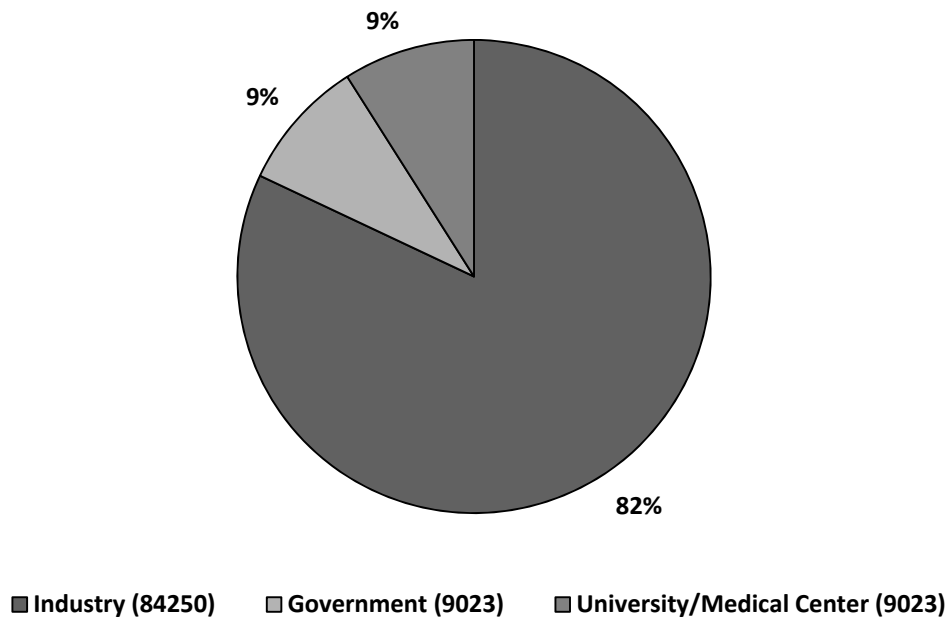
To calculate the percentage of all regulated animals subjected to UPAD, one needs to determine the total number of regulated animals used in any type of procedure. We did not independently calculate this figure from facility reports; the USDA's reported total is 2,134,182. If we adjust this figure downward by 15,884 (see previous number), we obtain 2,118,298. Of this total, 4.8% (102,384) were used in column E procedures (the USDA's figure is 5.6%).

According to our analysis, most of the animals reported in column E were guinea pigs (38%) and hamsters (36%) (Figure 1). In fact, guinea pigs and hamsters were used in column E procedures in far greater proportions than their overall usage would suggest (38% vs. 18% for guinea pigs, and 36% vs. 17% for hamsters). Conversely, all other regulated species (dogs, cats, rabbits, primates, farm animals, and "other") were used in column E procedures in far lesser proportions than their overall usage would suggest.

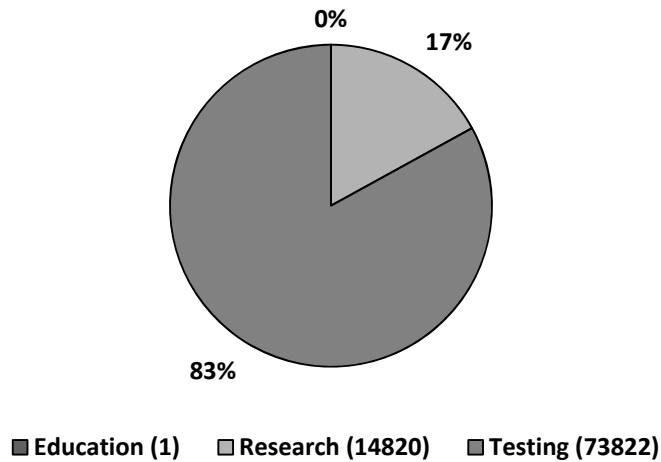
Approximately 80% of the animals subjected to UPAD were used by industry, with the remaining numbers being split fairly evenly between government facilities and universities/medical centers (Figure 2).

Some facilities failed to provide descriptions of column E procedure despite the AWA mandate to do so. Consequently, 13,741 animals (13%) could not be categorized according to type of use (research, testing, or education). Of the animals that could be categorized (88,643), 83% were used in testing and 17% were used in research (Figure 3). Only one animal was reported as used in an educational procedure. Given that the preponderance of column E use fell in the testing category, we decided to limit further analysis to procedures in this category.

**FIGURE 2** Types of facilities where USDA-regulated animals experienced unrelieved pain and distress during 1992. *N* = 102,384 animals.

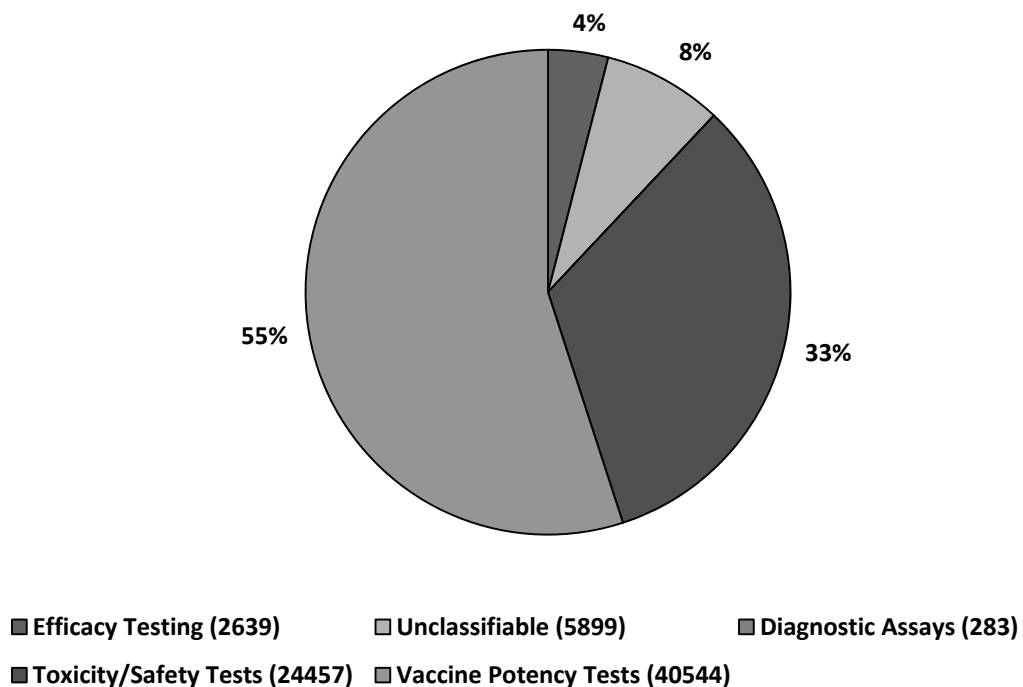


**FIGURE 3** Categories of procedures causing unrelieved pain and distress to USDA-regulated animals during 1992. N = 88,643.



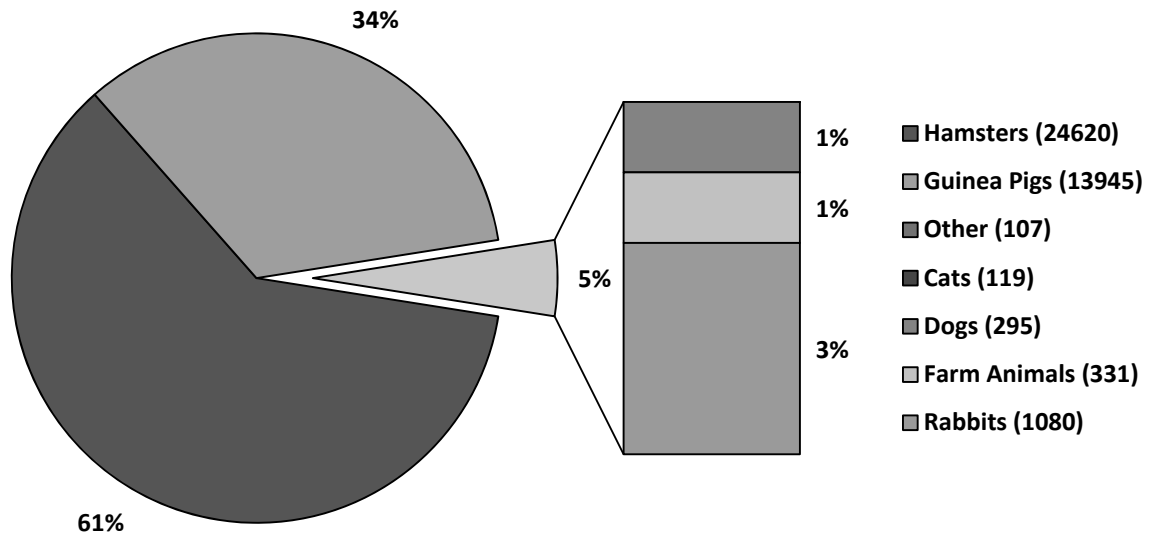
Of the 73,822 animals who experienced UP AD in testing procedures, vaccine potency testing alone accounted for 55% (Figure 4). Most of the remaining animals were involved in the heterogenous category of toxicity or safety tests. Unfortunately, column E descriptions typically were too brief and general to permit a more detailed analysis of the procedures involved.

**FIGURE 4** Types of testing procedures causing unrelieved pain and distress to USDA-regulated animals during 1992. N = 73,822.

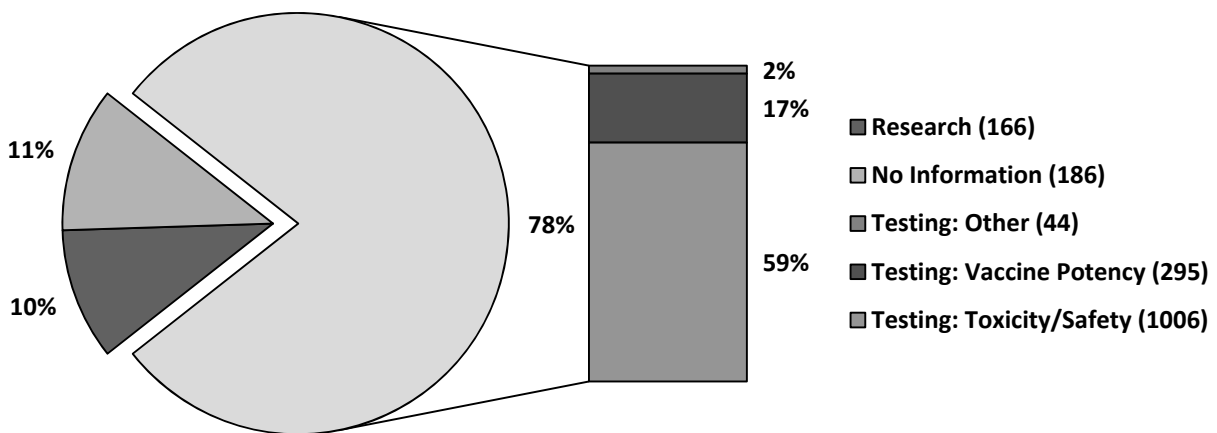




**FIGURE 5** Number of animals of various USDA-regulated species who experienced unrelieved pain and distress in vaccine potency testing during 1992. *N* = 40,544.



**FIGURE 6** Categories of procedures causing unrelieved pain and distress to dogs during 1992. *N* = 1,697.



Given the prominence of both vaccine potency testing (Figure 4) and the use of guinea pigs and hamsters (Figure 1) in column E procedures, it is not surprising that guinea pigs and hamsters accounted for the majority (95%) of the animals used in vaccine potency testing (Figure 5).

To this point, we have looked at species data only as far as they pertain to different categories of use. One can also look at the species data directly, and ask: "What is the full array of column E procedures to which species X is subjected?" Dogs reported in column E, for example, were used primarily in testing procedures and, in particular, the toxicity/safety testing subcategory (Figure 6).

## DISCUSSION

To our knowledge, this study is the only comprehensive exploration of data available in USDA facility reports on experimental procedures that cause UPAD in animals. Unfortunately, these reports do not enable us to generate a complete profile of procedures that cause UPAD, given the absence of systematic data on mice, rats, and nonmammalian species. We do not know the degree to which the patterns identified here are also representative of nonregulated (and nonreported) animals.

Even with respect to regulated species, however, several limitations inherent in the data should be kept in mind. First, levels of pain and distress experienced by the animals listed in column E were not reported; all that a column E listing indicates is that the actual level was more than slight or momentary. Consequently, the pain and distress could have been severe or moderate (perhaps even mild), or for any duration other than momentary. Second, column E data probably do not include all of the regulated animals that experienced moderate to severe pain and distress. Some of the animals reported in column D (pain relieved by drugs) probably experienced moderate to severe pain or distress, despite the drug administration. Because pain-relieving drugs were used, the animals were reported in column D, not E. Third, column E data may be underreported because some facilities are reluctant to reveal, in publicly available documents, that they did not administer pain-relieving drugs to animals in pain or distress. This reluctance may be reflected in the fact that only one animal was reported to have been subjected to UPAD in an educational procedure. In light of the shortcomings in the data, our strategy was to focus on overall patterns, not specific numerical results.

Notwithstanding these shortcomings, the USDA data are the only source of national statistics on pain and distress in the U.S. The analysis revealed that approximately 100,000 animals of regulated species were subjected to UPAD during FY92. The general patterns in column E usage were clear. Procedures involving UPAD were conducted primarily on guinea pigs and hamsters, and were not distributed evenly among fields and subfields of procedures, nor facility types. Most of the procedures fell into the testing category and vaccine potency subcategory and were carried out by industry.

The analysis highlights some of the ways that the USDA's current reporting system can be improved. In our opinion, the USDA should:

- Increase facility compliance with the "requirement" to provide descriptions of column E procedures.
- Increase the level of detail in these descriptions to enable reviewers to create a more detailed classification of experimental procedures.
- Revamp the current pain classification system, with its emphasis on pain-relieving drugs, into a true pain scale with graded levels of pain and distress.

- Expand the reporting system to include all species that the USDA has legislative authority to regulate (mammals and birds), particularly laboratory-bred mice and rats.

The analysis identified the categories of use that accounted for most of the column E procedures conducted on regulated species during 1992. All things being equal, painful procedures conducted on large numbers of animals should be considered priorities for research and development of alternative methods (Balls et al., 1995). Setting such priorities would maximize cooperation and efficiency among those working on-and financially supporting-alternatives development.

Setting priorities for alternatives development would also help facilitate a rational response to existing legislation. For example, the National Institutes of Health Revitalization Act of 1993 (Public Law 103-43) charged both the National Institutes of Health and the National Institute of Environmental Health Sciences with facilitating progress on the Three Rs; analyses such as the present one can assist these agencies in that process.

From the perspective of the Three Rs, the main finding of our analysis was that vaccine potency testing (VPT) accounted for a high percentage of the regulated animals who experienced UPAD. Hendriksen (C. Hendriksen, personal communication, May 29, 1996) found a similar result in an analysis of the more comprehensive national statistics in The Netherlands.

VPT essentially is a specialized form of efficacy testing. In the typical form of VPT, the animals are vaccinated and later "challenged" with the virulent microorganism or toxin. Potency testing is carried out on vaccines or "toxoids" for several diseases (e.g., pertussis, leptospirosis, rabies, polio, tetanus, and diphtheria). The procedures involve considerable pain and distress, as the assessments are typically based on death or severe clinical symptoms such as paralysis. VPT accounts for the majority of the animals used in vaccine quality control, which utilizes about 10% of the total number of animals used in all experimental procedures in the United Kingdom and The Netherlands (Hendriksen et al., 1994).

Hendriksen et al. (1994) discussed both the application of the Three Rs to VPT and the scientific shortcomings of existing animal tests in this field. Hendriksen and van der Gun (1995, p. 61) noted that, with respect to the use of animals in VPT, "we are still in a situation which does not differ greatly from that of 25 years ago." Fortunately, the field is becoming a priority for a number of scientists and organizations concerned with the Three Rs, including the Fund for the Replacement of Animals in Medical Experiments (R. Combes, personal communication, June 22, 1996). One facet of the refinement research on VPT involves the suitability of analgesics to these procedures (Van Loveren, Gianotten, Hendriksen, Schuurman, & Van Der Lann, 1994 ).

VPT follows guidelines promulgated by national and international regulatory authorities. In the present study, many of the facilities reporting VPT cited governmental regulations as the reason for conducting the procedure and for withholding pain relief. This suggests that regulatory requirements will need to be revised in order for alternative methods to be implemented.

It is difficult to say whether or not the overall patterns revealed in this study have changed much since 1992. We recommend that more recent data be analyzed. In the absence of more current information, however, the present analysis should be considered suggestive of current patterns, at least with respect to regulated species.

Judging from summary data in USDA annual reports, the percentage of animals in column E more than doubled from FY92 to FY94. This trend adds some urgency to the task of updating the present analysis.

## ACKNOWLEDGMENTS

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**<sup>1</sup>This figure exceeds the total number of research facilities registered with the USDA during the year (n = 1,527; USDA, 1993) because some registrants have more than one "site," and sometimes the individual sites, rather than the parent facility, submit reports.**

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