

SEARCHING FOR THE 3Rs: FACILITATING COMPLIANCE IN THE BIBLIOGRAPHIC SEARCH FOR ALTERNATIVES*

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Abstract: The search for alternatives is a requirement in several countries, but rarely are the logistics or the scientists' concerns considered. At the University of California Center for Animal Alternatives (UCCAA) we offer workshops on the nine UC campuses, teaching researchers, IACUCs, and librarians how to approach the alternatives search, including search strategy, appropriate terminology, and database suggestions/links. We are also developing a web-based resource along these same lines. Scientists generally approach an alternatives search as they approach any search; they search Medline, using the terms with which they are most conversant, and consider that this is adequate. However, there are several free bibliographic databases which are both appropriate and readily accessible, including Medline, Agricola and Toxline. A growing number of alternatives databases are available; these are rarely accessed by the scientific community. Websites such as AltWeb, Invitox and AWIC provide a virtually untapped wealth of information. There are also free government research sites which provide information on current research, such as CRIS, CRISP, and CORDIS. The terms used are equally as important as the database selection. Searching with the single keyword "alternatives" is less than adequate. Synonyms in all three areas of alternatives- replacement, reduction and refinement- must be developed and employed, such as anesthesia and analgesia, enrichment and husbandry, stress and distress. By offering concrete advice and assistance, as is included in our workshop curricula and on our website, the scientists can more easily perform worthwhile alternatives searches. By making use of the new technologies to create web-based search templates specific to the scientists' needs, we can help make the searching easier while also more relevant.

Introduction

The UC Center for Animal Alternatives was created by the University of California Office of the President due to a mandate by the California Legislature. Our purpose is to be a systemwide resource for all nine campuses in the University of California system, a single location collecting, housing, and disseminating information on alternatives to the use of animals in research. We are physically located at UC Davis in the School of Veterinary Medicine.

This paper focuses on the bibliographic search for alternatives to the use of animals in research, teaching, and testing. As medical and veterinary librarians,

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you understand the intricacies of literature searching. However, perhaps you are less familiar with the area of animal alternatives, and unaware that research scientists at our facilities have information needs that are not adequately being met. Though a medical and veterinary librarian at UC Davis for many years, I did not learn of this alternatives literature search requirement until I came to the Center three years ago. In order to understand the search and the requirements, I will provide you with a short overview of the issue; it will also provide the context for this regulation which affects us all so directly.

Alternatives Legislation

The Principles of Humane Experimental Technique is a book which was first published in 1959. It was written by two British researchers, William Russell and Rex Burch, who were the first to advocate the 3Rs in animal research: Replacement, Reduction, and Refinement. The book and the subject were fairly well ignored for about 25 years, after which time it was rediscovered and has since become the basis and the common language used in the discussion of alternatives.

The 3Rs that these British scientists brought into the vernacular stand for replacement, reduction, and refinement. Replacement is the replacement of animals with non-animal models or techniques. Reduction is reducing the number of animals used. Reduction can be achieved by quality literature searches, appropriate statistical design, use of pilot studies to estimate variance, use of transgenics, and changes in toxicological testing. Refinement is a technique or procedure to reduce pain and distress. Refinement offers the best opportunity for immediate implementation, and is the least often considered. Proper use of analgesics and anesthetics, knowledge of the test species' physiology and behaviors, modifications in restraint, handling, and blood collection techniques, and proper training of personnel all constitute refinements.

In the United State, it is the Animal Welfare Act, enacted in 1966, which legislates animal welfare. It started out as very basic legislation, but has continued to be amended, each time becoming more definitive, more specific and more restrictive. The 1985 amendment was called the "Improved Standards for Laboratory Animals Act"; it stated that pain and distress must be minimized in experimental procedures, and that alternatives to such procedures must be considered by the Principal Investigator. The 1989 amendment expanded on this by stating that the PI must consider not just alternatives, but all three Rs. This last amendment is 11 years old, yet this requirement to consider alternatives before any animal research can proceed is still controversial.

For members of the European Union, the European Directive states that the use of alternatives, where possible, is a legal requirement. This same requirement is also incorporated into the Convention for the Protection of Vertebrate Animals Used for Experimental and other Scientific Purposes by the Council of Europe.

"An experiment shall not be performed if another scientifically satisfactory method of obtaining the result is sought, not entailing the use of an animal, is reasonably and practicably available."

Together with the Codes of Practice on the Housing and Care of Laboratory Animals, the Animals (Scientific Procedures) Act clearly defines appropriate use and appropriate consideration of alternatives to the use of animals in the UK.

"The Secretary of State shall not grant a project licence unless he is satisfied (a) that the purpose of the programme to be specified in the licence cannot be achieved satisfactorily by any other reasonably practical method not entailing the use of protected animals; and (b) that the regulated procedures to be used are those which use the minimum number of animals, involve animals of the lowest degree of neurophysiological sensitivity, cause the least pain, suffering, distress or lasting harm, and are most likely to produce satisfactory results."

The UK and USA are not the only countries legislating animal welfare. Legislation is worldwide, and even though they may be members of the European Union and follow the European Directive, member states such as France, Germany, Italy, Netherlands, Norway, Sweden, and Switzerland have additional, supplemental legislation, requiring even further consideration of animal welfare and alternatives in animal research. Countries not in the European Union, such as Australia, New Zealand, and Japan also have legislation covering the care and use of experimental animals.

In response to the UK requirement, librarian Krys Bottrill at FRAME, which is the Fund for the Replacement of Animals in Medical Experiments, created A Guide to Searching for Alternatives to the Use of Laboratory Animals (<http://www.frame-UK.demon.co.uk/guide/index.htm>). It is designed for the researcher, intended to assist them in performing quality searches for alternatives. Dr. Bottrill's guide is an extremely thorough and useful resource, one which explains and instructs, as well as guides the user. In addition to the guide, she has also offered workshops for UK scientists on this topic.

Search Strategy

We have established that most countries require the use of alternatives to painful and stressful procedures when alternatives are available. In order to determine if such alternatives exist, researchers are expected, and often times required, to search the literature. This is where we medical and veterinary librarians enter the picture. While leaders in their respective areas, scientists are not expert in bibliographic searching, nor should they be expected to be. We are the information professionals. We can help them find the information or teach them the best strategy to find the information themselves. There is an approach to searching for alternatives which will provide the best hope of locating relevant information, but it is important to remember that you will not always find alternative methods which can be implemented in the research. The most basic thing to remember is that the alternatives for which we are required to search include all 3Rs, meaning replacement, reduction, and refinement, and not just replacement. The next two essentials may be intuitive to you, but are less so to our faculty. A thorough list of synonyms must be developed and the appropriate databases must be searched.

When working on library research, identify the search terms specific to your field of study, search as usual, peruse and identify anything relevant to 3Rs - in vitro, less evolved species, anesthesia and analgesia, statistical methods, etc. Then perform a second search to further investigate the 3Rs, by adding alternatives concepts and synonyms. You must use the appropriate terms which will be most helpful in searching for each R. Beginning a search with a list of possibly useful terms specific to alternatives can be extremely helpful. (Table 1) Subject headings such as Animal Welfare and Animal Testing Alternatives exist but are less than useful because most articles are not indexed as such. Searching by these subject headings tends to retrieve articles with a broad discussion of the issue as opposed to useful suggestions on alternative methods. Keyword and synonym searching is the most productive approach. Is there an analgesia available which won't interfere with the experimental results, is there a caging arrangement which will make the animal more comfortable, is there an enrichment device which will make the animal less fearful or less bored? The 3Rs are very open ended and any improvement at any level would be considered an "alternative".

Alternatives search terminology

alternativ*	husbandry
analges* or sedativ*	interactive
anesthe* or anaesthe*	method*
animal* test* alternat*	model*
anxiolytic*	postop* or postsurg*
artificial*	replace*
assay* or technique*	restrain*
behavi* enrich*	sedat*
computer* imag*	simulat*
culture	teach*
environ* enrich*	train* or educat*
euthanasia	video
handling	virtual
housing	vitro
	welfare or pain or stress or distress

Table 1

In addition to search terms, it is imperative to search in the appropriate database. While Medline is an excellent database and should be searched, it does not index all of the world's literature. Multiple database searches are required if the search is to be done in good faith. (Table 2) Agricola and Toxnet are two free databases you are probably familiar with. Agricola is particularly good because it indexes some of the more obscure publications, including the journals Animal Welfare and Alternatives to Laboratory Animals. Toxnet is an essential database for any toxicological research or protocol. CORDIS, CRIS, and CRISP all provide information on research funded by governmental grants. NORINA is the Norwegian Inventory of Alternatives which is a unique and comprehensive database of alternatives used in education.

Free Databases

AGRICOLA	CORDIS	Medline
CRIS		NORINA
CRISP		TBASE
		TOXNET

Table 2

There are additional databases that should be searched, dependent on the subject and protocol. (Table 3) Some of these databases you will have available to you free of charge, others available only for a price. You may also have other useful resources at your institution that I do not have listed here. In any event, legislation is not usually concerned with the expense of locating information; if the

investigator is working with sturgeon, Aquatic Sciences and Fisheries Abstracts should be searched. Proposals using exotic animals or reptiles should always be searched in Zoological Record for information on husbandry and behavior. PsycInfo provides a wealth of information on refinement, especially enrichment. Computer Articles and INSPEC should be searched whenever there is a possibility of computer modeling. Each database may have a use depending on the research and/or the animal.

Additional Bibliographic Databases

ABI	Fish & Fisheries
ASFA	INSPEC
BIOSIS	Lexis-Nexis
CAB	PsycINFO
CC	Sociological Abs.
Computer Art.	Web of Science (ISI)
Dissertation Abs.	Zoological Abs.
ERIC	

Table 3

There are animal welfare and alternatives organizations, as well as government-sponsored animal care groups, that provide extremely useful information and access to resources via their websites. (Table 4) AltWeb is a website located at the Center for Alternatives to Animal Testing at Johns Hopkins University in the US; they have taken the lead in organizing a centralized database for alternatives information. Governmental animal welfare organizations include ANZCCART for Australia and New Zealand, AWIC in the US, and CCAC in Canada. ECVAM, ICCVAM, and Invitox are databanks of invitro techniques in toxicology collected in Europe and the US. The list of helpful sites is long, most of which are linked from the UCCAA website (http://www.vetmed.ucdavis.edu/Animal_Alternatives/main.htm).

Other Resources

AltWeb	ICCVAM
ANZCCART	INVITTOX
AWIC	ILAR
CCAC	NCA
FRAME	UCCAA

Table 4

Embedded Search Templates

Another way we have found to assist the researcher is through the use of embedded search templates. An embedded search gives one the ability to store a search strategy as a link, to later click on the highlighted term, and rerun the search in real time. This means that anytime the link is clicked, the most recent citations in that database will be retrieved. This technology is ideal for repetitive searches, but what is unique is that more than one person could make use the same search. Anytime a researcher is using mice, alternatives to painful or stressful procedures, analgesia, anesthesia, and euthanasia must be searched. To have a site which maintains commonly needed searches so that any scientist could click and get the most recent information, without knowing which database to search, without knowing the best search strategy, would be very useful. To create a template is a simple process of selecting a database, developing an effective search strategy, saving the search URL, and pasting that into a webpage as a link.

Since Agricola is a free database and indexes publications very relevant to the area of animal care, it is ideal for accessing via an embedded search. From the UCCAA webpage on Refinement of Research Methods with Mice, listed under Agricola are several embedded searches: blood sampling, enrichment, euthanasia, refinement, and welfare. The search strategy/html format is hidden behind the link. When the "Enrichment" link is clicked, the computer automatically goes to Agricola and performs a current search using the strategy that has been embedded. After a moment, the Agricola search results page appears, from where one can click and go to abstracts, full citations, etc.

PubMed (Medline) is another free database providing access to valuable alternatives information, and they even provide instructions on how to store a search strategy as a link. The directions show how to save the search strategy, once you have identified the best approach, whether it is to use MeSH terms, text terms, limits, or whatever. You then copy the appropriate URL and paste it into your website as a live link. Whenever clicked, a live search is begun and the most recent PubMed information retrieved. Again, from the webpage on Refinement of Research Methods with Mice, listed under PubMed (Medline) are examples of commonly needed searches: blood sampling, caging, enrichment, euthanasia, handling, refinement, stress, transgenics, and welfare. By clicking on "Enrichment", a live search in Medline is initiated, using the search strategy embedded in the link. These search results are just like with a regular Medline search where one can go to the abstracts, related articles, etc.

Partnerships and Local Support

Creating search templates makes aspects of the alternatives search much easier for the scientist as well as making it better by using good search strategy and searching in the correct databases. It not only assists the researchers with regulatory compliance, but also educates them on information retrieval. It shows, too, how helpful and knowledgeable librarians are, especially librarians at their particular institution. By partnering with their local, in-house librarian, the scientist not only gets the assistance of an information professional, but also a colleague familiar with their facility's unique strengths and resources. For example, UC Santa Cruz librarians, located on the coast, are going to know a lot more about the resources relevant to marine scientists than I am at Davis, an inland veterinary school. And I am going to be much more familiar with bovine mastitis than my colleagues located at the biomedical library in the very urban UCLA.

The bottom line is that alternatives searches are required for regulatory compliance, and there is a need for our expertise and an opportunity to expand our services for our primary clientele. Research scientists at our institutions need our assistance and expertise with these alternative literature searches, yet they remain silent. We need to reach out to this audience, let our institutional officials and animal oversight committees know that we are aware of the search requirements and are available for instruction and referrals. We can also offer our assistance directly to the researchers. Even though they think they already know everything, and have a difficult time admitting that they don't know much about searching and/or multiple databases, if we publicize our availability to help with these searches, offer workshops, create an informational website, or develop search templates specific to their needs, they will realize that we are there to assist them with all aspects of their research goals.

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