

Using MeSH to Search for Alternatives to the Use of Animals in Research

Marina Chilov
Konstantina Matsoukas
Nighat Ispahany
Tracy Y. Allen
Joyce W. Lustbader

ABSTRACT. Searching for alternatives to using animals in research is not a standard service currently offered by most medical research libraries. The goal of this article is to demystify this type of expert search for medical librarians and to do so using a language they know well, that of the Medical Subject Headings (MeSH) thesaurus. An attempt is made in this paper to discuss possible search strategies and to include examples of recommended approaches to searching—all in the context of the 3Rs of alternatives: Replacement, Refinement, and Reduction. doi:10.1300/J115v26n03_04 [Article copies available for a fee from *The Haworth Document Delivery Service*: 1-800-HAWORTH. E-mail address: <docdelivery@haworthpress.com> Website: <<http://www.HaworthPress.com>> © 2007 by *The Haworth Press, Inc.* All rights reserved.]

Marina Chilov, MLS (mz84@columbia.edu) is Reference/Monograph Collection Development Librarian; Konstantina Matsoukas, MLIS (km2056@columbia.edu) is Head of Reference and Education Coordinator; and Nighat Ispahany, MLS (ni12@columbia.edu) is Reference/Media Collection Development Librarian; all are at Augustus C. Long Health Sciences Library of Columbia University, 701 West 168th Street, New York, NY 10032. Tracy Y. Allen, MLS (tya2@columbia.edu) is Adjunct Instructor, CDM-Community Health, 601 West 168th Street, Suite 24; and Joyce W. Lustbader, PhD (jwl2@columbia.edu) is Adjunct Professor of Ob/Gyn, 630 West 168th Street, P&S 16-408; both at Columbia University Medical Center, New York, NY 10032.

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INTRODUCTION

In its policy statement on the “Role of Expert Searching in Health Sciences Libraries,” the Medical Library Association (MLA) lists “Research Design Support” as one of the high impact areas that may benefit from the assistance of an expert librarian searcher.¹ Assistance with discovering “alternative animal models” is one of the examples that MLA gives of this type of support, yet “searching for alternatives to using animals in research” is not a standard service currently offered by most medical research libraries. The goal of this article is to demystify this type of expert search for medical librarians and to do so using a language they know well, that of the Medical Subject Headings (MeSH) thesaurus.

BACKGROUND

At research centers in the United States, experimental protocols that involve the use of animals must be submitted to the Institutional Animal Care and Use Committee (IACUC) for approval.² In addition to their experimental protocol, researchers must submit to IACUC a search strategy showing that they have performed a comprehensive search of the literature for alternatives to the use of animals in their research. The reason for doing this is that: “The Animal Welfare Act (AWA) regulations require principal investigators to consider alternatives to procedures that may cause more than momentary or slight pain or distress to the animals and provide a written narrative of the methods used and sources consulted to determine the availability of alternatives, including refinements, reductions, and replacements.”³ In “The Principles of Humane Experimental Technique,”⁴ Russell and Burch discuss the removal of inhumanity “under the three broad headings of Replacement, Reduction, and Refinement,” which are the three Rs referred to above. In brief, these are:

- Replacement—substitute animal with non-animal methods or lower organisms

- Refinement—explore techniques and procedures to reduce pain and distress
- Reduction—minimize the number of animals used

In considering more humane alternatives, researchers are expected to translate the three Rs into their investigations of the existing scientific literature. The main provider of assistance and training in this area is the Animal Welfare Information Center (AWIC), which was established in 1986 and is part of the U.S. Department of Agriculture (USDA) National Agricultural Library (NAL). AWIC is mandated by the AWA “to provide information for improved animal care and use in research, testing, teaching, and exhibition.”⁵ One of AWIC’s functions is to provide search support to both researchers and librarians who are searching for alternatives, as well as offer on-site training seminars. One such seminar was conducted at Columbia University in February 2004. During the session, AWIC specialists worked with local librarians and widely recommended that scientists seek the help of librarians at their institution. This effort helped spawn the animal alternatives search service that is now in existence at Columbia University’s Health Sciences Library.⁶

OBJECTIVES/PURPOSE

Medical Subject Headings (MeSH), the National Library of Medicine’s controlled vocabulary thesaurus,⁷ will be used in this paper to illustrate how using a familiar controlled vocabulary is an effective way to conduct a literature search that addresses the concepts behind searching for alternatives. NLM’s MEDLINE database is only one of a number of databases that should be consulted when doing a comprehensive search for alternatives. Other databases include AGRICOLA, Biological Abstracts, INSPEC, PsycINFO, Aquatic Sciences & Fisheries Abstracts, CRISP (Computer Retrieval of Information on Scientific Projects), and more.⁸ However, MeSH search strategies can only be used in MEDLINE; other databases have their own thesauri for indexing, if any. Still, exploring the terminology using MeSH will allow the user to harvest keywords and index terms describing concepts that can then be used to search databases other than MEDLINE.

There are many challenges to developing a standardized approach to searching for alternatives, the most obvious of which is the fact that no two experimental protocols will ever be the same. Searching for alternatives requires a great deal of flexibility in searching method and the

willingness to combine various search techniques. An attempt is made in this paper to discuss possible search strategies and to include examples of recommended approaches to searching. Examples given will be as generic as possible and common themes will be highlighted where appropriate. In addition, selected search strategies, as well as frequently used MeSH terms (useful at various stages of the 3Rs search), will be presented in Appendix A and Appendix B, respectively. The Ovid Technologies, Inc. interface will be used to present search examples.

DEVELOPING THE SEARCH STRATEGY

Generally, the sequence of events that precede a search for alternatives is as follows. A research scientist submits an experimental protocol (new or renewal) to his or her institution's IACUC for review. If the literature search for alternatives described therein is inadequate, he or she is referred to the library's alternatives search service for assistance. (It should be noted that, with the increased popularity of the search service at Columbia University's Health Sciences Library, more and more scientists now meet with a librarian prior to submitting their protocol to IACUC in order to avoid unnecessary delays.) A librarian will work independently on the protocol before meeting with the researcher to explain the search process. Often, the librarian and the researcher will then expand upon the search strategy together. The researcher will be expected to review the retrieved set of articles, focusing primarily on the "Materials and Methods" section of each article.

To be able to conduct a reasonable search for alternatives, librarians must first be provided with the experimental protocol, which should include the following information:

- Research Topic
- Research Objective
- Research Methods

It is a combination of these three components, easily remembered as "TOM," that will be searched upon when trying to address each of the three Rs—Replacement, Refinement, and Reduction. As with any database searching, developing the "animal alternatives" search strategy is always an exercise in compromise; it is a matter of finding the middle ground between what you will gain or lose by selecting one search term

over another, by using certain Boolean operators, and by increasing or decreasing search precision and recall.

Search Strategies Addressing “Replacement”

For “Replacement,” the goal of the search is to look for research studies that are similar to the experimental protocol in overall objectives and outcomes, but that may use non-animal methods or employ animals of lower species.

There are several ways that this goal can be translated into the literature search. The following case study will be used to illustrate the issues that the searcher should consider:

Assume that the objective of an experimental protocol is to study how retinoblastoma protein, a tumor suppressor, affects the process of carcinogenesis in lung cancer. The protocol involves inducing lung cancer in guinea pigs by means of cancer cell transplantation.

To begin the search, the broadest possible search is performed on the research topic (see Figure 1, sets #1-3) using the experimental protocol to identify terminology. Notice that the MeSH term “Neoplasms” is used instead of the more specific term, “Lung Neoplasms,” and that MEDLINE’s explode function is used “to retrieve citations that carry the specified MeSH heading (or subheading) and also retrieve citations that carry any of the more specific MeSH headings (or subheadings) indented beneath it in the Tree structure.”⁹ The idea behind this broad search is to retrieve research studies that share a similar research topic/objective, regardless of, in this case, the specific type of cancer being studied. Increasing the pool of studies similar in topic and objective will increase the likelihood that among such studies a potential animal alternative will be identified.

Substituting animal with non-animal models/methods. Once the initial broad research topic/objective search is done, the issue of “Replacement” can be addressed. The Boolean operator “OR” can be used to create a single search set of all articles indexed with either the “Animals” or “Humans” MeSH terms (see Figure 1, sets #4-7). The Boolean operator “NOT” is then applied to the search in order to exclude these articles from the final results set of citations (see Figure 1, set #7). As such, this final set of articles should hopefully include everything but animal or human experimentation with regard to this topic. (Note that excluding the articles indexed with the term “Humans” also excludes

FIGURE 1. Excluding Research Studies That Use Animals and Humans

#	Search History
1	exp Neoplasms/
2	exp Tumor Suppressor Proteins/ or exp Genes, Tumor Suppressor/
3	1 and 2
4	exp Animals/
5	Humans/
6	4 or 5
7	3 not 6

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studies involving, for example, human umbilical vein endothelial cells, which could be used as an *in vitro* screening assay. The Boolean operator “NOT” should always be used with caution as its use involves the risk of missing some potentially useful studies.)

Another way to approach this type of search is to create a search strategy using MeSH terms that actually describe the possible non-animal methods themselves. This strategy can include, for example, the MeSH terms “Computer Simulation,” “Cadaver,” “Aborted Fetus,” etc. (see Figure 2, sets #4-13). It is important to note, however, that the same MeSH terms cannot always be used for every protocol. Ideally, the terms included should be ones that are applicable to the experimental protocol at hand and that actually would be considered by the researcher as an alternative technique.

Exploring the MeSH hierarchy is a good way to compile terminology for other possible alternative models/methods. For example, the MeSH terms found under the broader heading “Models, Theoretical” could be utilized if these are deemed to be applicable to a protocol (see Figure 3). Take note, however, that the “Models, Theoretical” MeSH hierarchy includes the “Disease Models, Animal” MeSH term which should be excluded from the “Replacement” search (whose aim it is to locate animal model *alternatives*). The rest of the headings found under “Models, Theoretical” should also be used with caution as articles indexed with these terms may include both animal and non-animal models.

One of the complications that searchers may encounter when using MeSH terms is that non-animal methods used in protocols are not always used in the exclusion of animal techniques; a protocol may progress from the *in vitro* stage to *in vivo* within the same experiment. As a

FIGURE 2. Including Research Studies That Employ Possible Non-Animal Models/Methods

#	Search History
1	exp Neoplasms/
2	exp Tumor Suppressor Proteins/ or exp Genes, Tumor Suppressor/
3	1 and 2
4	exp Models, Theoretical/
5	exp Disease Models, Animal/
6	4 not 5
7	Computer Simulation/
8	Cadaver/
9	Aborted Fetus/
10	exp Culture Techniques/
11	exp Cells, Cultured/
12	in vitro.pt.
13	6 or 7 or 8 or 9 or 10 or 11 or 12
14	3 and 13

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result, a citation may be indexed with “in vitro.pt.” and “Animals” at the same time. For example, if an experiment used cultured cells *derived* from mice, MeSH terms “Mice” and “Cells, Cultured” would both be applied to the citation by NLM indexers.¹⁰

Consequently, combining the two approaches to searching (described in Figures 1 and 2) with a Boolean operator “OR” is recommended to avoid missing potentially useful citations. Keep in mind that when searching the literature for alternatives to the use of animals in research, the nature of the search is such that it will inevitably be one of high recall and low precision. It is expected that the researcher will end up with a large number of citations that he or she will have to review, few of which will actually be relevant. It is necessary to be this comprehensive, however, in order for the researcher to be able to make the claim that all possible alternatives were considered.

Substituting animal with “lower” organisms (less-sentient species). If non-animal replacements are not available, substituting animals with phylogenically “lower” organisms is also an option. Such a search can be achieved, for example, in the above-mentioned case study, by exploding the MeSH term “Animals” and then excluding from that results set all

FIGURE 3. Sample MeSH Hierarchy for Possible Alternative Models

<input checked="" type="checkbox"/>	Models, Theoretical
	<input type="checkbox"/> Fractals
	<input type="checkbox"/> Fuzzy Logic
[-]	<input type="checkbox"/> Models, Biological
	<input type="checkbox"/> Disease Models, Animal
	<input type="checkbox"/> Models, Cardiovascular
	<input type="checkbox"/> Models, Genetic
	<input type="checkbox"/> Models, Immunological
[+]	<input type="checkbox"/> Models, Neurological
	<input type="checkbox"/> Models, Chemical
	<input type="checkbox"/> Models, Educational
	<input type="checkbox"/> Models, Molecular
	<input type="checkbox"/> Models, Nursing
	<input type="checkbox"/> Models, Organizational
[+]	<input type="checkbox"/> Models, Psychological
[+]	<input type="checkbox"/> Models, Statistical
	<input type="checkbox"/> Nonlinear Dynamics

of the articles indexed with the MeSH term “Mammals” (see Figure 4, sets 4-6). This example assumes that non-mammal subjects would be reasonable alternatives for this research protocol. Once this set is combined with the Boolean operator “AND” to the broad topic/objective search set, studies in this area that are using phylogenically lower species will be retrieved (see Figure 4, sets 1-7). In another case, for example, if the researcher was experimenting on primates, a “lower” organism substitute could be one from the rodentia order. (Note that the rodentia order is also from the mammal class.)

Alternatively, if the researcher is already aware of potential “lower” organism candidates for substitution, these can be searched upon directly using the MeSH terms that describe them and then combined together in one search set using the Boolean operator “OR.” For example, the researcher may wish to consider “Guinea Pigs” or “Rabbits” (see Figure 5) as possible substitutes. When using subject headings for organisms, it is generally advisable to choose a broader heading over the species-specific one in order to increase the pool of potential alternatives. In this last example, the broader headings were the names of the orders that include “Guinea Pigs” and “Rabbits,” which are “Rodentia” and “Lagomorpha,” respectively. This set of possible alternative organisms would then be combined to the broad research topic set using the Boolean operator “AND.”

Search Strategies Addressing “Refinement”

For “Refinement,” the goal of the search is to locate research studies that are similar to the experimental protocol in overall objectives,

FIGURE 4. Excluding Phylogenically “Higher” Organisms

#	Search History
1	exp Neoplasms/
2	exp Tumor Suppressor Proteins/ or exp Genes, Tumor Suppressor/
3	1 and 2
4	exp Animals/
5	exp Mammals/
6	4 not 5
7	3 and 6

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FIGURE 5. Sample MeSH Hierarchy for Possible Phylogenically “Lower” Organisms

[-]	<input type="checkbox"/>	Vertebrates	
	[+]	<input type="checkbox"/> Amphibia	
	[+]	<input type="checkbox"/> Birds	
	[+]	<input type="checkbox"/> Fishes	
	[-]	<input type="checkbox"/> Mammals	
		[+]	<input type="checkbox"/> Artiodactyla
		[+]	<input type="checkbox"/> Carnivora
		[+]	<input type="checkbox"/> Cetacea
			<input type="checkbox"/> Chiroptera
			<input type="checkbox"/> Elephants
			<input type="checkbox"/> Hyraxes
		[+]	<input type="checkbox"/> Insectivora
		[-]	<input checked="" type="checkbox"/> Lagomorpha
			<input type="checkbox"/> Hares
			<input type="checkbox"/> Rabbits
		[+]	<input type="checkbox"/> Marsupialia
		[+]	<input type="checkbox"/> Monotremata
		[+]	<input type="checkbox"/> Perissodactyla
		[+]	<input type="checkbox"/> Primates
		[-]	<input checked="" type="checkbox"/> Rodentia
			<input type="checkbox"/> Chinchilla
			<input type="checkbox"/> Dipodomys
			<input type="checkbox"/> Gophers
			<input type="checkbox"/> Guinea Pigs

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outcomes, and even animal model used, but that may use more humane or less painful methodology and procedures.

Unfortunately, there are no terms in the MeSH thesaurus designed to assist researchers in evaluating the humaneness of one experimental technique over another. The studies that would likely be useful in identifying these more humane procedures generally will not include a direct assessment of the methods used (in terms of humaneness). There is, of course, an exception to this—articles that directly address the concepts of experimental ethics and the humane treatment of animals in research. Citations for these articles could include some of the MeSH terms shown in Figure 6. Articles indexed with MeSH terms such as “Animal Experimentation,” for example, may be valued by the researcher as they would allow him or her to gain additional insights into the ethical, legal, and social considerations of experimenting on animals.

Two ways that an experimental protocol can be “more humane” are (1) by using alternatives to painful and unreasonably invasive procedures (substituting procedures), or (2) by finding ways of reducing pain and distress while performing the painful/invasive procedure (improving on procedures). How these two approaches can be translated into a literature search is described in the examples that follow.

Substituting procedures. Without the availability of index terms that rate humaneness, researchers are left with little choice but to conduct a broad search on their topic and objective with the intent of finding experiments very similar to their own. This will allow them to compare their own proposed protocol with the protocols of studies with a similar experimental design. By reading the “Materials and Methods” sections of these articles, the researcher may come across a variation in approach that may be “more humane” than their own proposed way of doing things.

The idea behind this first refinement-type search is to look for studies that employ alternatives to the procedures that the researcher intends to use. It is not unlike the type of comprehensive search that a researcher would perform to establish the uniqueness of his or her work, to ensure

FIGURE 6. Examples of MeSH Terms that Address the Concepts of Animal Welfare and the Humane Treatment of Animals in Research

MeSH Subject Headings	<ul style="list-style-type: none"> * <u>Animal Care Committees</u> * <u>Animal Experimentation</u> / <u>es [Ethics]</u> * <u>Animal Use Alternatives</u> * <u>Animal Welfare</u>
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that already existing research will not be duplicated, and to become familiar with any relevant/related pre-existing research studies. This type of refinement search strategy, however, should be developed without using any terminology describing the specific experimental methods intended to be used in the protocol.

For example, in Figure 7, the intentionally broader MeSH term “Neoplasms, Experimental” is chosen in the search (for substitute procedures for inducing carcinogenesis in animals) even though the aim of this search is to retrieve studies describing more specific methods—possibly ones that the researcher was previously unaware of. If more specific terminology is used in the search strategy instead, the scientist would not have the opportunity to discover new approaches that were not considered when the protocol was originally being written. Assuming neoplasm transplantation is the technique that the researcher initially intended to use in his or her experimental protocol, in order to exclude this intended neoplasm induction method from the final search set of possible procedures, the MeSH term “Neoplasm Transplantation” would then be combined with the MeSH term “Neoplasms, Experimental” using the Boolean operator “NOT” (see Figure 7, sets #1-6).

On the other hand, if a scientist does have some ideas for possible alternatives based on his or her familiarity with the field, he or she may choose to search directly on those. For example, a researcher who initially planned to perform an invasive surgery on a pregnant animal in order to introduce modified genetic material to the fetal airways may consider some less invasive surgical procedures. Searching on the MeSH tree “Surgical Procedures, Minimally Invasive” (see Figure 8) will enlighten him or her of some available options (including, for example, fetoscopy) and enable him or her to find relevant studies.¹¹

FIGURE 7. Excluding Research Studies That Use the Intended Procedure

#	Search History
1	exp Tumor Suppressor Proteins/ or exp Genes, Tumor Suppressor/
2	exp *Lung Neoplasms/
3	exp Neoplasms, Experimental/
4	exp Neoplasm Transplantation/
5	3 not 4
6	1 and 2 and 5

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FIGURE 8. Sample MeSH Hierarchy for Possible Substitutes to “Less Humane” Procedures

[-]	<input checked="" type="checkbox"/>	Surgical Procedures, Minimally Invasive
	[-]	<input type="checkbox"/> Endoscopy
		<input type="checkbox"/> Angioscopy
		<input type="checkbox"/> Arthroscopy
		<input type="checkbox"/> Bronchoscopy
		<input type="checkbox"/> Colposcopy
		<input type="checkbox"/> Culdoscopy
		<input type="checkbox"/> Cystoscopy
	[+]	<input type="checkbox"/> Endoscopy, Digestive System
		<input type="checkbox"/> Fetoscopy
		<input type="checkbox"/> Hysteroscopy
	[+]	<input type="checkbox"/> Laparoscopy
		<input type="checkbox"/> Laryngoscopy
		<input type="checkbox"/> Mediastinoscopy
		<input type="checkbox"/> Neuroendoscopy
	[+]	<input type="checkbox"/> Thoracoscopy
		<input type="checkbox"/> Ureteroscopy
	[+]	<input type="checkbox"/> Video-Assisted Surgery

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Beyond the primary experimental method used (e.g., neoplasm induction—the principal method used for achieving the main objective in the first case study discussed in this article), other procedures employed at different stages of the protocol should also be considered for refinement. Blood collection, drug injection, animal identification, and surgical

procedures are all common techniques that should be scrutinized by the researcher and evaluated for their humaneness. As mentioned previously, searching on a broader MeSH term can be a productive way for the researcher to uncover alternative procedures that he or she may not have previously considered because he or she was unaware of them. For example, if an animal protocol involves ear tagging as a method of animal identification, searching on the MeSH term “Animal Identification Systems” combined with the MeSH term that describes the animal type (class, order, species, etc.) will return articles on ear-tagging techniques, as well as other options that differ from the ones that the researcher originally intended to use.

In another example, if a researcher concluded that, rather than injecting an experimental animal repeatedly, a more humane drug delivery alternative would be to utilize implantable infusion pumps, he or she could search on this substitute procedure directly by using the MeSH term “Infusion Pumps, Implantable/ae, ve [Adverse Effects, Veterinary].” Combining this term with the MeSH term “Guinea Pigs,” for example, is the way to uncover articles wherein the “Materials and Methods” sections document how this intervention is used with this type of animal. After reviewing these articles, the researcher would then be in a position to better evaluate whether the new method would be a feasible alternative for his or her proposed experimental procedure.

A note of caution should be made about using the broader MeSH term “Models, Animal” without first studying the MEDLINE database scope notes for terms in this hierarchy. Each term in this hierarchy has a limited scope and as such, it is recommended that these terms be combined with the exploded term “Animals” using the Boolean operator “OR.” This approach is taken in order to avoid missing out on potentially relevant articles that may only be indexed with one of these terms (see Figure 9, sets #4-6).

An example of a citation¹² where “Animals” and “Rats” were used as descriptors instead of the MeSH term “Models, Animal” (or any of the narrower MeSH terms in that hierarchy) is provided in Figure 10.

Improving on procedures. If the searcher discovers that there are indeed no alternatives to certain necessary procedures, then a second refinement-type search must be performed, this time using the names of the materials and methods (proposed to be used in the research protocol) for the search terminology. Combining this search with the specific animal type that the researcher intends to use is advisable to limit the search results set to studies that are most relevant to the original research proto-

FIGURE 9. Using the “Animals” and “Models, Animal” MeSH Hierarchies

#	Search History
1	exp Tumor Suppressor Proteins/ or exp Genes, Tumor Suppressor/
2	exp *Lung Neoplasms/
3	1 and 2
4	exp Animals/
5	exp Models, Animal/
6	4 or 5
7	3 and 6

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FIGURE 10. Example Citation Illustrating the Use of the Term “Animals” in MeSH Indexing

Tsujiuchi T, Sasaki Y, Konishi Y, Tsutsumi M. Alterations of the retinoblastoma-related gene RB2/p130 in lung adenocarcinomas induced by N-nitrosobis(2-hydroxypropyl)amine in rats. [Journal Article. Research Support, Non-U.S. Gov't] *Molecular Carcinogenesis*. 35(2):57-62, 2002 Oct.

MeSH Subject Headings [Adenocarcinoma / ci \[Chemically Induced\]](#)
[*Adenocarcinoma / ge \[Genetics\]](#)
[Adenocarcinoma / me \[Metabolism\]](#)
[Animals](#)
[Blotting, Northern](#)
[Blotting, Western](#)
[DNA Mutational Analysis](#)
[DNA Primers / ch \[Chemistry\]](#)
[Genes, Retinoblastoma](#)
[Lung Neoplasms / ci \[Chemically Induced\]](#)
[*Lung Neoplasms / ge \[Genetics\]](#)
[Lung Neoplasms / me \[Metabolism\]](#)
[Male](#)
[*Mutagens / pd \[Pharmacology\]](#)
[*Nitrosamines / to \[Toxicity\]](#)
[*Phosphoproteins / ge \[Genetics\]](#)
[Phosphoproteins / me \[Metabolism\]](#)
[Polymorphism, Single-Stranded Conformational](#)
[*Proteins](#)
[RNA, Messenger / me \[Metabolism\]](#)
[Rats](#)
[Rats, Wistar](#)
[*Retinoblastoma Protein / ge \[Genetics\]](#)
[Retinoblastoma Protein / me \[Metabolism\]](#)
[Retinoblastoma-Like Protein p130](#)
[Reverse Transcriptase Polymerase Chain Reaction](#)

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col. Again, the idea behind this search is to find experiments that performed a procedure or technique in a more humane way.

Assume that the researcher is looking for better ways to relieve the pain and distress that the animal experimental subject may experience

as a result of an operative surgical procedure. One approach to searching would be to search using the name of the intended procedure (e.g., using the MeSH term “Lymph Node Excision”) and to qualify this subject heading with relevant subheadings. These could include: “Methods,” “Adverse Effects,” “Rehabilitation,” etc. The resulting search set would then be combined using the Boolean operator “AND” to a MeSH term that describes the specific type of animal being used (e.g., “Dogs”).

Approaches to refinement can be as varied as the methods used in research—they are innumerable. Surgical procedures, instrumentation, and equipment; postoperative complications and care; veterinary care; animal handling and housing; anesthesia and analgesia; euthanasia; and many other issues may be in question when it comes to their degree of humaneness. Each of these elements of the research materials and methods, no matter how mundane, should be examined and addressed individually in the search for alternatives.

Search Strategies Addressing “Reduction”

For “Reduction,” the goal of the search is to search for research studies that are similar to the experimental protocol in overall objectives, outcomes, animal model used, and even methodology, but that may use a smaller number of animals to achieve the same outcomes.

Unfortunately, there are no MeSH terms specifically intended to describe the number of animals used in an experimental protocol, and no MeSH terms with which indexers could indicate that the minimum number of animals was used. The search addressing the issue of reduction is consequently a targeted one in which the searcher should include terminology that describes all three components provided in the protocol—the research topic, objective, and materials and methods. The researcher will subsequently be required to browse the “Materials and Methods” section of each article retrieved in order to uncover the number of animals used in each study.

FUTURE CONSIDERATIONS AND RECOMMENDATIONS FOR IMPROVING INDEXING

MEDLINE indexing currently includes terms that specify research type (e.g., “in vitro.pt.”) or research subject (e.g., “Animals”); however, the list is incomplete. The present indexing could definitely benefit from

the creation of more descriptive and precise terminology. For example, establishing a new MeSH term to better characterize the *ex vivo* type of research would facilitate searching as researchers often do differentiate between *in vitro*, *in vivo*, and *ex vivo* research.

Another improvement that would aid the searcher looking for alternatives would be if the authors of the research studies themselves would disclose in the “Materials and Methods” section of the article whether their choice of methodology had been made because it was less invasive or more humane. Ideally, this information would also be reflected in the keywords supplied by the author and used to direct indexers to assign terms that would help searchers to identify these articles. A similar suggestion to this was made in the report that followed the 2003 International Workshop on Alternative Methods to Animal Experiments.¹³

CONCLUSION

Searching for alternatives to the use of animals in research involves the type of database searching skills that most medical librarians already possess. With a minimal investment of time in professional development, medical librarians can become extremely proficient at performing these searches. There is much to be gained by offering this type of expert search service. It provides an ideal way for librarians to promote their value to their institution by helping its researchers meet the Animal Welfare Act legal requirement, and consequently, making them a part of the institution’s grant/award application process.

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REFERENCES

1. Medical Library Association. “Medical Library Association Policy Statement: The Role of Expert Searching in Health Sciences Libraries.” (September 2003). Available: <http://www.mlanet.org/resources/expert_search/policy_expert_search.html>. Accessed: October 27, 2006.
2. Institutional Animal Care and Use Committee (IACUC). “A Comprehensive Resource for Animal Care and Use Committees.” (Copyright 2000, Last update: May 23, 2006). Available: <<http://www.iacuc.org/>>. Accessed: October 27, 2006.

3. Animal and Plant Health Inspection Service, Animal Care Program. "Animal Care Resource Guide, Policy #12: Alternatives to Painful Procedures." (June 21, 2000). Available: <<http://www.aphis.usda.gov/ac/policy/policy12.pdf>>. Accessed: October 27, 2006.
4. The Johns Hopkins Center for Alternatives to Animal Testing. "The Principles of Humane Experimental Technique," by W.M.S. Russell and R.L. Burch. (1959). Available: <http://altweb.jhsph.edu/publications/humane_exp/het-toc.htm>. Accessed: October 27, 2006.
5. Animal Welfare Information Center (AWIC). "AWIC Web Site." (Last Modified: Aug 17, 2006). Available: <<http://awic.nal.usda.gov/>>. Accessed: October 27, 2006.
6. Chilov, M., and Matsoukas, K. "Library Support of an Academic Medical Center's Institutional Animal Care and Use Committee (IACUC)." Poster presented at the Annual Meeting of the Medical Library Association, May 2005, San Antonio, TX.
7. National Library of Medicine. "Fact Sheet: Medical Subject Headings (MeSH®)." (September 1, 1999, Last Updated: May 27, 2005). Available: <<http://www.nlm.nih.gov/pubs/factsheets/mesh.html>>. Accessed: October 27, 2006.
8. Animal Welfare Information Center. "Conducting Literature Searches: Addressing the Search for Alternatives." Available: <<http://www.nal.usda.gov/awic/alternatives/Altbrochure.pdf>>. Accessed: October 29, 2006.
9. National Library of Medicine. "PubMed Tutorial Glossary." (Last Updated November 4, 2005). Available: <http://www.nlm.nih.gov/bsd/pubmed_tutorial/glossary.html#auto_explode>. Accessed: October 27, 2006.
10. Foltyn, V.N., and Golan, T.D. "In Vitro Ultraviolet Irradiation Induces Pro-inflammatory Responses in Cells from Premorbid SLE Mice." *Lupus* 10, no. 4 (2001): 272-83.
11. Peebles, D.; Gregory, L.G.; David, A. et al. "Widespread and Efficient Marker Gene Expression in the Airway Epithelia of Fetal Sheep after Minimally Invasive Tracheal Application of Recombinant Adenovirus in Utero." *Gene Therapy* 11, no. 1 (January 2004): 70-8.
12. Tsujiuchi, T.; Sasaki, Y.; Konishi, Y.; and Tsutsumi, M. "Alterations of the Retinoblastoma-Related Gene RB2/p130 in Lung Adenocarcinomas Induced by N-Nitrosobis(2-hydroxypropyl)amine in Rats." *Molecular Carcinogenesis* 35, no. 2 (October 2002): 57-62.
13. Grune, B.; Fallon, M.; Howard, C. et al. "Report and Recommendations of the International Workshop 'Retrieval Approaches for Information on Alternative Methods to Animal Experiments.'" *Altex-Alternativen Zu Tierexperimenten* 21, no. 3 (2004): 115-27.

APPENDIX A

Selected Useful Search Strategies or “Hedges”

Replacement Hedges:		
Topic	Hedge(s)	Combine Sets
I. Topic/Objective Search	2. exp Animals/ or exp Models, Animal/ 3. Humans/	4. 2 or 3 5. 1 not 4
I. Topic/Objective Search	2. exp Models, Theoretical/ 3. exp Disease Models, Animal/ 5. Computer Simulation/ or Cadaver/ or Aborted Fetus/ 6. exp Culture Techniques/ or exp Cells, Cultured/ or in vitro.pt.	4. 2 not 3 7. 4 or 5 or 6 8. 1 and 7
I. Topic/Objective Search	2. exp Mammals/	3. 1 not 2
Refinement Hedges:		
Topic	Hedge(s)	Combine Sets
I. Topic/Objective Search	2. exp Animals/ 3. exp Models, Animal/	4. 2 or 3 5. 1 and 4
I. Search on animal type and/or search on a procedure	2. exp *Anesthesia and Analgesia/ 3. exp *Central Nervous System Depressants/ 4. exp *Sensory System Agents/	5. 2 or 3 or 4 6. 1 and 5
I. Search on animal type and/or search on a procedure	2. exp Intraoperative Complications/ 3. exp Postoperative Complications/ 4. exp Perioperative Care/ 5. complications.fs.	6. 2 or 3 or 4 or 5 7. 1 and 6
I. Search on animal type	2. exp Animal Welfare/	3. 1 and 2
I. Search on animal type	2. Euthanasia, Animal/	3. 1 and 2

APPENDIX B

Selected MeSH Terms (Frequently Used in Searching for 3 Rs)

Please note that MeSH terms that predominantly cover ethical, legal, and regulatory aspects of animal use in biomedical research are recommended as supplemental to searching on the research topic, objectives, and materials and methods of a research protocol (TOM). MeSH terms that cover animal anatomy and veterinary handling of animals are (on the most part) not used for indexing articles that are using animals as a means to prove the value of a procedure in humans or to prove the efficacy of a drug. These terms help in finding articles on procedures done on animals (the animals being the “objective” of the study described) which is why they are also recommended for supplemental use.

MeSH Hierarchies	Notes
Anesthesia and Analgesia/	
Animal Diseases/	(supplemental use)
Animal Structures/	(supplemental use)
Animal Welfare/	(supplemental use)
Animals/	
Behavior, Animal/	(use for certain animal types)
Biomedical Research/	
Cells, Cultured/	
Central Nervous System Depressants/	
Genetic Vectors/	
Housing, Animal/	(use for certain animal types)
Intraoperative Complications/	
Investigative Techniques/	
Models, Theoretical/	
Pain/	
Perioperative Care/	
Peripheral Nervous System Agents/	
Postoperative Complications/	
Retroviridae/	
Social Environment/	(use for certain animal types)
Specimen Handling/	
Surgical Procedures, Operative/	
Veterinary Medicine/	(supplemental use)
Individual MeSH	Notes
Animal Husbandry/	(supplemental use)
Computer Simulation/	
Laboratory Animal Science/	(supplemental use)
Pregnancy, Animal/	
Veterinary Drugs/	(supplemental use)
MeSH Subheadings	Notes
/Adverse Effects	
/Anatomy & Histology	(supplemental use)
/Methods	
/Physiology	(supplemental use)
/Psychology	(supplemental use)
/Rehabilitation	
/Surgery	(supplemental use)
/Veterinary	(supplemental use)