Session 4.2
Information retrieval – search strategies and search engines

Alternative Search Methods to Retrieve Information on the Web

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Summary
It is difficult to retrieve relevant scientific information on alternative methods to animal use. Since 1992, the National Library of Medicine (NLM) has made efforts to improve access to its bibliographic collection on animal use alternatives. In 2001, the NLM began ALTBIB, an online version of previously developed bibliographies. The NLM also added several key journals on alternatives to animal use to MEDLINE/PubMed, and added some relevant new MeSH terms. The ALTBIB search interface has been enhanced to allow searches conducted in MEDLINE/PubMed through a search strategy filter tailored for alternatives. This interface enables users to find the latest citations.

Keywords: alternative methods, database, information retrieval, search strategy, Internet, MEDLINE, PubMed

Introduction

The scientific community is sensitive to concerns about how and why animals are used in biomedical research and testing. Although alternatives to methods based on the use of animals may not satisfy all the requirements of the biomedical research communities, alternatives to the use of vertebrates have been developed and validated. Research on such methodologies is aimed at refining procedures to reduce pain and discomfort, reducing the number of animals required to provide scientifically valuable results, and replacing live vertebrates when an alternative methodology can be verified and validated by the scientific community (the 3Rs).

NLM's ALTBIB (Hudson et al., 2002) is a searchable bibliographic collection on alternatives to animal testing. It includes citations from published articles, books, book chapters, and technical reports from 1992 to 2001. Citations were selected manually after searching various NLM bibliographic databases. The selection of citations involved further review and verification by subject specialists to ensure relevance and quality. The bibliography features citations concerning methods, tests, assays, and procedures that may prove useful in establishing alternatives to the use of intact vertebrates.

In 2001, several enhancements were made to MEDLINE to facilitate the information retrieval of animal alternatives literature. These included the addition of new MeSH main headings on the animal alternatives subjects. Several important journals relevant to animal alternatives were added to the journals indexed for MEDLINE. Since the introduction of these enhancements in MEDLINE and MeSH, ALTBIB has not been updated. Believing that users would be able to search and retrieve directly from MEDLINE/PubMed, it was decided that the effort to manually curate an extensive bibliography was no longer justifiable. Furthermore, the manually created bibliography was limited by the fact that it was never current, but rather became obsolete as soon as produced.

Later study (Grune et al., 2002) showed that the literature relevant to animal alternatives was not easily retrievable. While the new MeSH terms were used, on the whole, to indicate the topics discussed in the citation, many relevant articles would not be

indexed with the new terms. Obtaining relevant information on animal alternatives from MEDLINE/PubMed remains an ongoing problem. Search strategies for animal alternatives have been developed, and incorporated in the ALTBIB search interface. This paper describes the method of developing the search strategy.

Materials and methods

A method was developed to formulate a MEDLINE/PubMed search strategy from MeSH headings assigned in key journal citations. The following steps were taken, in the order indicated:

1. Identify the key journals

MEDLINE/PubMed search was performed using the MeSH heading "Animal Use Alternatives". Search results were downloaded, and the journal title field was extracted, sorted and ranked by frequency. The frequencies were normalised with the total count of citations from each journal.

2. Retrieve all citations from key journals

A MEDLINE/PubMed search with the query using the Journal Title mnemonics "TA" as qualifiers was performed:
Altern Lab Anim[TA] OR ALTEX[TA] OR Toxicol In Vitro[TA] OR ILAR J[TA]

3. Extract and rank MeSH headings by frequency

A Unix shell script was used to extract the MH (MeSH heading) field from all the citations retrieved in steps 1 and 2. The MeSH headings were then sorted and ranked by frequency in descending order.

4. Extract top-ranked relevant MeSH headings

The list of frequency-ranked MeSH headings was examined to find and eliminate terms that were "check tags" (e.g. Human, Animal) or very non-specific terms (e.g. Time Factors, Reproducibility of Results). The top ranking MeSH headings were examined by a subject expert, and descriptors related to animal alternatives were identified.

5. Find co-occurring MeSH headings for general terms

Some of the frequently occurring MeSH headings were quite general. If these MeSH headings were to be included in the search strategy, they needed to be coordinated with other MeSH headings (and qualifiers). To find the coordinating MeSH headings for these general terms, co-occurring MeSH headings were extracted, sorted, and ranked by frequency. For example, the important concept of pain and distress in animals could be expressed with co-ordinated MeSH indexing: (Pain OR Stress, Psychological) AND Animal Welfare.

6. Formulate a search strategy

A search strategy was formed by concatenating the MeSH headings and expressions. In addition to the MeSH headings and expressions, relevant journal titles were also included. All the terms were combined with the Boolean operator OR.

7. Incorporate search strategy to ALTBIB interface

The ALTBIB search interface was then enhanced to allow searches in MEDLINE/PubMed. One or more user-specified query terms are combined with the search strategy with the Boolean operator "AND". Additional search "Limits" were provided to narrow the searches for citations published in 2000-2005, "Animal Use Alternatives" indexed citations, and toxicology subsets. In addition, the "Edit Search Strategy" page allows users to modify or add terms to the search strategy.

Results

The key journals were identified by analysing the search results of "Animal Use Alternatives". The highest frequency journals with citations indexed with "Animal Use Alternatives" included: *Alternatives to Laboratory Animals, ALTEX, Toxicology In Vitro*, and *ILAR Journal* (see tab.1).

Over 5000 citations were retrieved from a search within these 10 key journals.

The citations were downloaded in MEDLINE format, using the MEDLINE/PubMed "Send to File" feature. MeSH headings were extracted from the citations. They were sorted and ranked by frequency of occurrence.

Following the steps outlined above, a collection of high frequency relevant MeSH headings and expressions, and coordinating MeSH headings was developed. To formulate the final search strategy, the MeSH headings and expressions were combined. Key journal titles were also added to ensure the inclusion of citations from these journals. Boolean operator OR bundled the search terms together to form the final search strategy (see tab. 2).

Tab. 1: Frequency journals are indexed with "Animal Use Alternatives"

	Frequency of "Animal Use Alternatives" Index	Total count of citations in this journal	Normalised frequency
Alternatives to Laboratory Animals	234	350	0.668
ATLA Abstracts	8	19	0.421
Society and Animal	4	15	0.267
ALTEX	101	464	0.217
Toxicology *In Vitro*	68	575	0.118
In Vitro & Molecular Toxicology	4	53	0.075
ILAR Journal	23	305	0.075
Developments in Biologicals (Basel)	27	515	0.052
Journal of Applied Animal Welfare Science	3	88	0.034
Developments in Biological Standardisation	99	2983	0.033

Searches in ALTBIB to MEDLINE/PubMed were formulated to combine the search terms with the search strategy. For example, for a search of "Up and Down Procedure", the query to MEDLINE/PubMed was formed as:

"Up and Down Procedure" AND (*In vitro*[mh] OR cell lines[mh] OR cells, cultured OR 3t3 cells OR animal use alternatives OR animal testing alternatives OR animal experimentation OR animal welfare OR laboratory animal science/mt OR animal rights OR animal housing OR animal care committees OR ((pain OR psychological stress) AND animal welfare) OR animal husbandry OR toxicity tests/mt OR toxicology/mt OR tetrazolium salts OR neutral red OR comet assay OR LLNA OR mutagenicity tests OR mutagens/tox OR carcinogens/tox OR teratogens/tox OR animals, laboratory OR QSAR OR structure activity relationship OR ALTEX[TA] OR ILAR J[TA] OR Toxicology[TA] OR Toxicol In Vitro[TA] OR Toxicol Lett[TA] OR Reprod Toxicol[TA] OR Toxicol Sci[TA] OR Food Chem Toxicol[TA] OR Hum Exp Toxicol[TA] OR Regul Toxicol Pharmacol[TA] OR Altern Lab Anim[TA] OR Arch Toxicol[TA] OR Contemp Top Lab Anim Sci[TA] OR Lab Anim NY[TA] OR ATLA Abstr[TA] OR Environ Health Perspect[TA] OR Toxicol Pathol[TA] OR Fundam Appl Toxicol[TA] OR Soc Anim[TA] OR In Vitr Mol Toxicol[TA] OR Dev Biol Basel[TA] OR J Appl Anim Welf Sci[TA] OR Dev Biol Stand[TA] OR J Vet Med Educ[TA] OR (Vaccines AND Animal Use Alternatives) OR (Antibodies, Monoclonal/biosyn AND (Hybridomas OR Bioreactors).

As a result of these efforts, it is now possible to use the ALTBIB search interface to do a selective search for citations in PubMed involving the particular area of interest combined with a broad search strategy to identify those citations of particular interest for alternatives to animal use.

Discussion and conclusion

Efforts by the NLM to improve information about animal alternatives have been going on since 1992. The first efforts resulted in the ALTBIB database, containing over 7,500 citations on tests and methods that refine, reduce, or replace animal experimentation. However, the process used to create this bibliography could not support the increasing amount of information available. Review and verification by subject specialists was necessary to ensure the relevance of the citations. As the explosion of information in the biomedical fields progressed, the human effort involved in the review process became unsupportable.

Furthermore, a major limitation of producing a selective bibliography such as this is that the resulting bibliography is limited by time. It cannot accommodate new materials in a timely manner, but instead remains a static picture, perhaps subject to periodic updates.

In 2001, NLM made several additional efforts to improve access to information about animal alternatives. Knowing that indexing practices could never identify all the articles relevant to animal alternatives, certain concepts seemed of sufficient maturity to add as MeSH headings. These added headings would facilitate indexing of journal citations in which some of the animal alternatives concepts were discussed.

Additionally, after a meeting at NLM, and on the recommendation of representatives from the scientific community, several journals especially focused on animal alternatives were added to those indexed for MEDLINE.

A recent study by ZEBET indicated that the current indexing systems do not provide the required information, since not all of the relevant information is indexed under "alternative methods". The development of suitable search strategies on alternative methods was recommended by representatives of animal welfare information centres.

Search strategy retrieval of animal alternatives information from MEDLINE/PubMed was developed by the NLM ALTBIB team. It has been incorporated into the new ALTBIB interface. The search strategy provides an alternative way of providing relevant information to the animal alternatives community.

In addition to using the search strategy method, there are other methodologies that could be applicable to animal alternatives information retrieval on the Web. Table 3 summarises the various approaches to supporting information access.

Tab. 2: Search strategy terms grouped by categories

Category of concepts	MeSH expressions
In Vitro	(*In Vitro* [MH]) (Cell Lines [MH]) (Cells, Cultured [MH]) (3T3 Cells)
Animal Alternatives	(Animal Use Alternatives) (Animal Testing Alternatives) (Animal Experimentation)
Animal Welfare	(Animal Welfare) (Laboratory Animal Science/methods) (Animal Rights) (Animal Housing) (Animal Care Committees) ((Pain OR Psychological Stress) AND Animal Welfare) (Animal Husbandry)
Methods / Reagents	(Toxicity Tests/methods) (Toxicology/methods) (Tetrazolium Salts) (Neutral Red) (Comet Assay) (LLNA) (Mutagenicity Tests)
Toxicological Concepts	(Mutagens/toxicity) (Carcinogens/toxicity) (Teratogens/toxicity)
Animals	(Animals, Laboratory)
Structure-Activity	(QSAR) (Structure-Activity Relationship)
Journals	(ALTEX) (ILAR J) (Toxicol In Vitro) (Altern Lab Anim)(Contemp Top Lab Anim Sci) (Lab Anim (NY)) (ATLA Abstr) (Environ Health Perspect) (Toxicol Pathol) (Fundam Appl Toxicol) (Toxicology) (Toxicol Lett) (Reprod Toxicol) (Toxicol Sci) (Food Chem Toxicol) (Hum Exp Toxicol) (Regul Toxicol Pharmacol) (Arch Toxicol) (Soc Anim) (In Vitr Mol Toxicol) (Dev Biol Basel) (J Appl Anim Welf Sci) (Dev Biol Stand) (J Vet Med Educ)
Other	(Vaccines AND Animal Use Alternatives) (Antibodies, Monoclonal /biosyn AND (Hybridomas OR Bioreactors)

Tab. 3: Comparison of search methods on the Internet

	Level of Effort	Updates	Scope/Resources	Sustainability
Customised Bibliography	High. Continuously collect and review.	Tends to lag behind.	Single.	Low.
Search Strategy	Low to Moderate. Create search strategy initially, modify as needed.	Retrieves the most . current information	Single.	High.
Information Portal	Moderate. Identify and maintain list of Web resources. Make all participating sites searchable.	Retrieves the most current information.	Multiple Web resources. Only static pages are searchable.	Moderate.
Meta-search	Moderate. Identify and maintain list of Web resources. Configure initially.	Retrieves the most current information.	Multiple Web resources. Both static pages and hidden web (databases) are searchable.	High.

Information Portals

Information portals are collaborations among organisations to develop cross-organisation websites (portals) to provide the breadth of information and services available on a particular topic or audience group. An example of this work is the ALTWEB website (Hakkinen and Green, 2002). ALTWEB, collaborating with member institutions, offers a one-stop shop for animal alternatives information. The information portal provides a starting point, or a gateway, to other related resources. Collaboration among the participating organisations is crucial. While a portal organises information and provides links to the resources of the participating organisations, content or data integration could be a challenge. Information from heterogeneous sources should be made available to applications or users of the portal website.

Meta-Search and Clustering

Meta-search and clustering techniques have been developed using natural language processing methodologies. Target databases or Web information resources can be designated for a custom search. The search results are analysed, and concepts of interest are aggregated and clustered. Users may then refine or modify their queries. For example, at the National Library of Medicine, a meta-search and clustering engine has been developed to perform topic specific searches in areas of AIDS/HIV and toxicology/ environmental health information.

Future

NLM is committed to provide published information on methods that replace, reduce or refine animal use in scientific experimentation. Our goal is to refine search strategies, reduce the number of missed important papers, and replace the legacy information architecture with a new computing paradigm.

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Searching Strategies for Detecting Publications on Alternative Methods: A Pilot Study

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Summary
As a consequence of the increasing regulatory acceptance of the 3Rs concept of Russel and Burch (1959) on using alternative methods to animal experiments, it is essential that scientists, animal welfare officers, and public policy-makers are able to retrieve relevant, high-quality publications on alternative methods. Efficiently retrieved scientific literature will improve the application of alternative methods. In a pilot study we asked: What are effective search strategies for articles on alternative methods to acute oral toxicity testing? Free text searches (n=28) were performed in databases. The retrieval performance of selected search terms (n=17) was evaluated. We determined the relevance of the articles retrieved and identified a first ranking of search terms and databases for searching for articles on alternative methods used in acute oral toxicity testing. More research will be needed to address other areas of toxicity testing. Recommendations of search strategies to improve the success of searching for articles on alternative methods should include appropriate search terms, phrases and recommendations for databases.

Keywords: animal welfare, animal testing alternatives, databases, searching strategies, search terms

Introduction

In EU member states and in the USA, scientists are obliged by animal welfare legislation not to conduct an animal experiment if another scientifically satisfactory method to obtain the desired information is reasonably and practicably available (Council Directive 86/609/EEC, United States Department of Agriculture, 1997; United States Department of Agriculture, 2000).

To meet the regulatory obligation to use alternatives to experimental animals, scientists should consult literature and other relevant sources on alternatives prior to any experimental study using laboratory animals. It is the responsibility of each scientist to select the most appropriate database to obtain information on alternatives, which have been defined as methods that refine, reduce or replace animal experiments (The 3Rs Concept of Russell and Burch, 1959).

Animal welfare legislation in the European Union and the USA is the basis for information service systems supporting searches for alternative methods. It is essential that scientists, animal welfare officers, and public policy-makers can retrieve relevant, high-quality alternative methods reports. A wide range of information resources, e.g. databases and websites, offer scientific information on alternative methods (Hakkinen et al., 2002). Scientists expect to obtain accurate, complete and relevant information within a short time frame by using online sources, including web-based bibliographic databases and specialised web sites.

Of course, it is in the highest interest of the information provider and information services such as ZEBET, the National German Center for Documentation and Evaluation of Alternative Methods to Animal Experiments, to ensure that the relevant information is readily accessible, especially literature on animal welfare regulations and public health service policies.

However, in our Internet era, the problem is not how to distribute information but rather how to find the right information within an appropriate time frame. This discussion has focused on the problem of information retrieval in the heterogeneous environment of the World Wide Web (Krause, 2002; Adamczak et al., 2002).

In November 2003, at the international workshop, "Retrieval Approaches for Alternative Methods to Animal Experiments" in Berlin, representatives of European and U.S. information centres recommended the development of web-based search tools to improve the information retrieval of alternative methods from the Internet (Grune et al., 2004). Search tools should include search algorithms with suitable search terms. Web-based search tools for alternative methods should allow the use of the most specific search profile reflecting the type of research to which alternative methods are to be applied. Furthermore, searches based on multi-database formats as well as recommendations for databases supporting appropriate searching strategies should be discussed.

Since 1989, ZEBET's information service has responded to inquiries from universities, individual scientists, animal welfare offices and the general public. In 2000, ZEBET introduced AnimAlt-ZEBET, an internet database on alternatives to animal experiments (Grune et al., 2000). Based on ZEBET's experience in documentation, indexing and searching for alternative methods, we endeavoured to answer the question: What are effective strategies to search for articles on alternative methods in databases?

In October 2004, ZEBET began a pilot study focused on information retrieval on alternative methods for testing the acute oral toxicity of chemical and pharmaceutical substances as a

replacement of the "classic" LD_{50}-test. The objective of the pilot study was to translate ZEBET's know-how in documentation, indexing and information retrieval into recommendations for searching strategies to find information on alternative methods in databases.

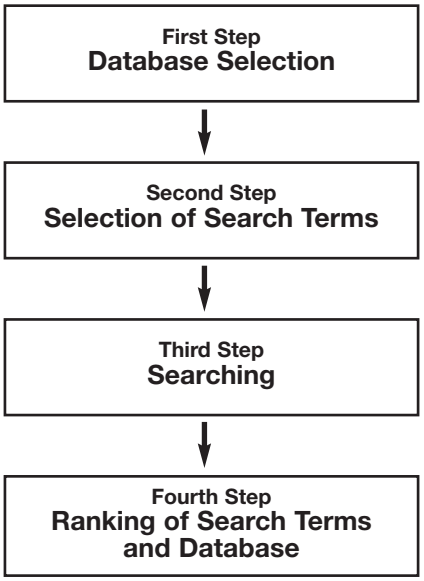
Methods

This study was conducted at the ZEBET, the National German Center for Documentation and Evaluation of Alternative Methods to Animal Experiments, at the German Federal Institute for Risk Assessment between October 2004 and April 2005. A multidisciplinary team of investigators, including scientists and information professionals, undertook this study.

For searching, we used DIMDI, the official host of biomedical databases and provider of medical information systems within the German Federal Ministry of Health, http://www.dimdi.de. DIMDI, the German Institute of Medical Documentation and Information, provides comprehensive scientific data from international publications in the fields of medicine, pharmacology, toxicology and biology. DIMDI offers access to about 70 literature databases, full text databases, as well as factual databases with approximately 100 million documents.

We arranged three database pools based on DIMDI's selection by frequency, two of which consisted of free-of-charge databases and one consisted of commercial, charging databases. Searching was conducted in a superbase mode, which means that all selected databases were searched simultaneously. Altogether, we conducted 28 single free-text searches in preselected databases. Retrieval performance of 17 selected search terms was evaluated. We determined the relevance of the articles retrieved and identified a ranking of search terms and databases for searching for articles on alternative methods to acute oral toxicity testing.

Our investigation consisted of four steps summarised in the following flow chart (see fig. 1):



First Step: Database selection

DIMDI offers a database selection tool called DIMDI Index. Databases were selected based on the frequency of retrieved documents on the comprehensive topic of acute toxicity testing. First, we marked the following relevant subject groups for the index: Human Medicine (all relevant databases), Pharmacology (all relevant databases), Toxicology (all relevant databases), Biotechnology, Genetic Engineering, Medical Devices, Veterinary Medicine.

After marking relevant subject groups, we entered the following search term combination: (acute and tox?)/same sent). This search term combination allowed a broad pre-selection of all databases with information on the topic of acute toxicity. The symbol "?" is a variable truncation. Each question mark is replaced by an arbitrary number of letters. The command ".../same sent" searches for documents in which the search terms "acute" and "tox?" are placed in the same sentence. In that way, we retrieved all documents, in which both search terms were used in close relation. We got an overview of the number of hits resulting from our inquiry in the individual databases, including free-of-charge databases and commercial databases. We selected the following three database pools for searching, based on the retrieved DIMDI Index specific for the topic of acute toxicity.

The first database pool, made up of 11 free-of-charge databases, consisted of a total of 21,014,273 documents on December 9, 2004 and 21,020,203 documents on December 12, 2004. The first database pool contained the following databases: ZT00 – AnimAlt-ZEBET; CL63 – CancerLit; CA66 – CATFILEplus; KL97 – Kluwer-Verlagsdatenbank; ME0A – MEDLINE Alert; ME60 – OLDMEDLINE; ME66 – MEDLINE; SM78 – SOMED; SPPP – Springer-Verlagsdatenbank; TV01 – Thieme Verlagsdatenbank;T165 – XTOXLINE.

The second database pool, made up of 23 free-of-charge databases, consisted of a total of 22,436,740 documents on January 10, 2005. The second database pool contained the following databases: ZT00 – AnimAlt ZEBET; CC00 – CCMed; CL63 – CancerLit; CA66 – CATFILEplus; CDSR 93 – Cochrane Library – CDSR; CDAR 94 – The Cochrane Database of Abstracts of Reviews of Effectiveness; AR 96 – Deutsches Ärzteblatt; GM 03 – gms; GA03 – gms Meetings; HN 69 – HECLINET; INAHTA – NHS-CRD-HTA; KR 03 – Karger Verlagsdatenbank; KL97 – Kluwer-Verlagsdatenbank; LWW04 – LWW-Verlagsdatenbank; MK77 – MEDIKAT; ME0A – MEDLINE Alert; ME60 – OLDMEDLINE; ME66 – MEDLINE; SM78 – SOMED; SPPP – Springer-Verlagsdatenbank; SP97 – Springer-Verlagsdatenbank; TV01 – Thieme-Verlagsdatenbank; T165 – XTOXLINE.

The third database pool, made up of 21 commercial, charging databases, consisted of a total of 69,741,166 documents on February 7, 2005. The third database pool contained the following databases: CB85 – AMED; AN83 – Adis Newsletters; BA70 – BIOSIS Previews; CV72 – CAB Abstracts; CCTR93 – Cochrane Library – Central; BD82 – Derwent Biotechnology Resource; DH64 – Derwent Drug Backfile; DD83 – Derwent Drug File; EA08 – EMBASE Alert; EM74 – EMBASE; EB94 – Elsevier BIOBASE; FS69 – FSTA; AZ72 – GLOBAL Health; HA85 – HAD; HT83 – IHTA; IA70 – IPA; II78 – ISTPB + ISTP/ISSHP; MT68 MEDITEC; NHSEED – NHS-EED; IS74 – SciSearch; TB69 – TOXBIO.

Second Step: Selection of search terms

We searched a total of 17 terms: one specific search term for the topic of our investigation concerning acute oral toxicity, 10 general terms for alternative methods and animal welfare, and 6 relevant biomedical search terms. We selected exclusive search terms in English, since the majority of relevant literature is published in English, including abstracts and keywords.

The selection of search terms was based on the terms of the Medical Subject Headings thesaurus (MeSH), the index terms of AnimAlt-ZEBET-Database, and definitions of professional associations.

AnimAlt-ZEBET documents have been evaluated by ZEBET's staff according to the 3Rs principle; the documents provide an assessment of the current stage of development, validation and acceptance of the methods for regulatory purposes. Each document is characterised by specific keywords and includes abstract and bibliographic references. ZEBET's index terms correspond to those of MeSH. MeSH is a controlled vocabulary produced by the National Library of Medicine (NLM) and used for indexing, cataloguing, and searching for biomedical and health-related information and documents.

● Search term for the topic of acute oral toxicity

ZEBET's pilot study focused on information retrieval on alternative methods for testing the acute oral toxicity of chemical and pharmaceutical substances as a replacement of the classic LD_{50}-Test. This topic was chosen because there are clear definitions for acute toxicity as well as for acute oral toxicity. In addition, there are well-published alternative methods and five documents in the AnimAlt-ZEBET database.

The MeSH term "Acute Toxicity Tests" is defined by the NLM (2005) as follows: Experiments designed to determine the potential toxic effects of one-time, short-term exposure to a chemical or chemicals.

Acute toxicity studies include different test procedures, depending on the type of administration, e.g. acute oral toxicity, acute dermal toxicity or acute inhalation toxicity. As mentioned above, we searched literature for the topic of alternative methods for acute oral toxicity testing. The Organisation for Economic Co-operation and Development (OECD) defines "Acute oral toxicity" as: the adverse effects occurring within a short time of oral administration of a single dose of a substance or multiple doses given within 24 hours (OECD, 1993). The principle of the LD_{50} test is to dose groups of animals with a single dose of a test substance at concentrations expected to cause death in at least a fraction of the animals dosed (OECD, 2002).

AnimAlt-ZEBET contains five alternative method documents for acute oral toxicity testing, in which the term "acute oral toxicity" is used (AnimAlt-ZEBET, 2005):

- Determination of the approximative LD_{50} for testing the acute toxicity of pharmaceutical substances as a replacement of the classic LD_{50}-test
- Up-and-down procedure for testing the acute oral toxicity of chemicals with a significantly reduced number of solely female rats as a replacement of the classical LD_{50} test
- Fixed Dose Procedure for testing the acute oral toxicity of chemical substances as a replacement of the classical LD_{50} test
- Acute Toxic Class Method for testing the acute oral toxicity of chemicals as a replacement of the classical LD_{50} test
- Determination of the starting dose for acute toxicity (LD_{50}) testing of chemical substances by applying linear regression models of "The Registry of Cytotoxicity"

● Search terms for alternative methods and animal welfare

The selection of search terms for alternative methods and animal welfare is based on ZEBET's investigation of indexing systems of alternative methods in established literature databases, e.g. MEDLINE, Embase, Agris, CAB Abstracts, and Agricola (Grune et al., 2004; Meißner, 2002). We identified the following search terms for alternative methods and animal welfare corresponding to the 3Rs Concept of Russel and Burch:

- alternatives to animal testing
- animal testing alternative, animal testing alternatives
- animal testing reduction
- animal testing refinement
- animal testing replacement
- animal use alternatives
- animal use reduction
- animal use replacement
- animal use refinement
- animal welfare

The MeSH-Term "Animal Testing Alternatives" (1985-2000) is defined as: Procedures, such as tissue culture, mathematical models, etc., when used or advocated for use in place of the use of animals in research or diagnostic laboratories (National Library of Medicine, 2005). Since 2000, the term "Animal Use Alternatives" is used by the NLM as: Alternatives to the use of animals in research, testing, and education. The alternatives may include reduction in the number of animals used, replacement of animals with a non-animal model or with animals of a species lower phylogenetically, or refinement of methods to minimise pain and distress of animals used.

The MeSH explains the term "Animal Welfare" as: The protection of animals in laboratories or other specific environments and the promotion of their health through better nutrition, housing, and care. This may be carried out through legislation or regulation.

● Relevant biomedical search terms

In addition, we selected the following search terms, which are used in the scientific literature and in AnimAlt-ZEBET documents to describe alternative methods for acute toxicity testing:

- cell culture, cell cultures
- *in vitro*
- model
- method, methods
- procedure, procedures
- approach , approaches

Third Step: Searching

● Search modus

We used DIMDI ClassicSearch, the expert search modus for command language professionals. DIMDI ClassicSearch offers options to formulate search queries and provides comprehensive

access to all of DIMDI's databases. For example, we used truncated and qualifying search terms, combined search terms with logical operators, and modified their sequence using parentheses. Truncated search terms allowed to search several terms with one command, e.g. "animal test?", which covers animal testing alternative, animal testing alternatives, animal testing reduction, animal testing refinement, animal testing replacement.

• Search mode

We searched in free text search mode to find all available documents containing information on alternative methods in any accessible text field of the documents, e.g. title, keywords, abstract.

Fourth Step: Ranking of search terms and databases

The retrieval performances of selected search queries were evaluated according to the relevance of the content of documents retrieved for the topic of alternative methods for acute oral toxicity testing. Relevance has been evaluated and was confirmed by ZEBET's staff in comparison to AnimAlt-ZEBET documents, including references for alternatives for acute oral toxicity testing. From the number of retrieved relevant documents, we identified a first ranking of search terms and databases to search for articles on alternative methods to acute oral toxicity testing.

Tab. 1: Searching in the first database pool – 11 databases free-of-charge – December 2004

Search number	Date	Number of documents in total	Search queries acute oral tox AND ...	Retrieved documents	Relevant documents
1	09.12.2004	21,014,273	Acute Oral Tox? AND ALTERNATIV?	18	17
2	09.12.2004	21,014,273	Acute Oral Tox? AND ANIMAL TEST?	15	9
3	09.12.2004	21,014,273	Acute Oral Tox? AND ANIMAL USE	2	2
4	09.12.2004	21,014,273	Acute Oral Tox? AND ANIMAL WELFARE	10	10
5	09.12.2004	21,017,709	Acute Oral Tox? AND (CELL# AND CULT?/SAME SENT)	35	1
6	09.12.2004	21,017,709	Acute Oral Tox? AND VITRO	39	3
7	09.12.2004	21,017,709	Acute Oral Tox? AND MODEL?	31	10
8	12.12.2004	21,020,203	Acute Oral Tox? AND METHOD?	30	8
9	10.12.2004	21,020,203	Acute Oral Tox? AND PROCEDURE?	30	17
10	12.12.2004	21,020,203	Acute Oral Tox? AND APPROACH?	16	6
				226 Documents	**83 Documents**

Tab. 2: Searching in the second database pool – 23 databases free-of-charge – January 2005

Search number	Date	Number of documents in total	Search queries ((acute AND tox?)/ same sent) AND oral/same sent AND ...	Retrieved documents	Relevant documents
1	10.01.2005	22,436,740	((acute AND tox?)/same sent) AND oral/same sent AND alternativ?	29	25
2	10.01.2005	22,436,740	((acute AND tox?)/same sent) AND oral/same sent AND animal test?	27	11
3	10.01.2005	22,436,740	((acute AND tox?)/same sent) AND oral/same sent AND animal use	2	2
4	10.01.2005	22,436,740	((acute AND tox?)/same sent) AND oral/same sent AND animal welfare	13	13
5	10.01.2005	22,436,740	((acute AND tox?)/same sent) AND oral/same sent AND vitro	15	3
6	10.01.2005	22,436,740	((acute AND tox?)/same sent) AND oral/same sent AND model?	13	5
7	10.01.2005	22,436,740	((acute AND tox?)/same sent) AND oral/same sent AND method?	29	13
8	10.01.2005	22,444,599	((acute AND tox?)/same sent) AND oral/same sent AND procedur?	18	17
9	10.01.2005	22,436,740	((acute AND tox?)/same sent) AND oral/same sent AND approach?	25	5
				171 Documents	**94 Documents**

Tab. 3: Searching in the third database pool – 21 commercially charging databases – February 2005

Search number	Date	Number of documents in total	Search queries ((acute and tox?)/same sent) AND oral/same sent AND …	Retrieved documents	Relevant documents
1	07.02.2005	69,741,666	((acute AND tox?)/same sent) AND oral/same sent AND alternativ?	64	34
2	07.02.2005	69,741,666	((acute AND tox?)/same sent) AND oral/same sent AND animal test?	21	9
3	07.02.2005	69,741,666	((acute AND tox?)/same sent) AND oral/same sent AND animal use	8	8
4	07.02.2005	69,741,666	((acute AND tox?)/same sent) AND oral/same sent AND animal welfare	15	13
5	07.02.2005	69,741,666	((acute AND tox?)/same sent) AND oral/same sent AND vitro	13	6
6	07.02.2005	69,741,666	((acute AND tox?)/same sent) AND oral/same sent AND model?	23	8
7	07.02.2005	69,741,666	((acute AND tox?)/same sent) AND oral/same sent AND method?	72	18
8	07.02.2005	69,741,666	((acute AND tox?)/same sent) AND oral/same sent AND procedur?	14	12
9	07.02.2005	69,741,666	((acute AND tox?)/same sent) AND oral/same sent AND approach?	23	9
				253 Documents	**117 Documents**

Results

Number of retrieved and relevant documents

Results are presented on the number of retrieved and relevant documents for each search query and are summarised in three tables. The tables contain the search queries, number of the retrieved and relevant documents. The search profile was recorded for each search query.

Searching in the first database pool started with the fixed, and consequently more restricted, search query "acute oral tox?" (see tab. 1). Searching in the second and third database pool started with search term combination "((acute and tox? and oral)/same sent)", which allowed wider searching (see tab. 2 and 3). Next, search terms for acute oral toxicity were combined with terms for alternative methods and animal welfare.

Searching in the first database pool retrieved 226 documents, 83 of these were classified as relevant. In comparison, searching in the second database pool retrieved 171 documents of which 94 documents were relevant. Both database pools contained free-of-charge databases with a total number of documents between ca. 21 and 22 million. In general, the number of retrieved documents is very low in relation to the total number.

The third database pool contained exclusively databases charging a fee. In this pool, the number of ca. 70 million documents is clearly higher than in the pools of databases that offer

Tab. 4: Ranking of search terms used for searching in the first database pool – 11 databases free-of-charge

Ranking of search terms	Number of relevant documents
1. alternativ?	17
procedure?	17
2. animal welfare	10
model	10
3. animal test?	9
4. method?	8
5. approach?	6
6. *vitro*	3
7. animal use	2
8. cell#	1
cult?	1

Tab. 5: Ranking of search terms used for searching in the second database pool – 23 databases free-of-charge

Ranking of search terms	Number of relevant documents
1. alternativ?	25
2. procedur?	17
3. animal welfare	13
method?	13
4. animal test?	11
5. approach?	5
model?	5
6. *vitro*	3
7. animal use	2

Tab. 6: Ranking of search terms used for searching in the third database pool – 21 commercially charging databases

Ranking of search terms	Number of relevant documents
1. alternativ?	34
2. method?	18
3. animal welfare	13
4. procedur?	12
5. approach?	9
animal test?	9
6. animal use	8
model?	8
7. *vitro*	6

Tab. 7: Ranking of databases in the first database pool – 11 databases free-of-charge

Ranking of databases	Number of relevant documents
1. MEDLINE, ME66	43
2. AnimalAlt-ZEBET, ZT00	29
3. SOMED, SM78	9
4. XTOXLINE, TI65	2

Tab. 8: Ranking of databases in the second database pool – 23 databases free-of-charge

Ranking of databases	Number of relevant documents
1. MEDLINE, ME66	52
2. AnimalAlt-ZEBET, ZT00	25
3. MEDLINE Alert, ME0A	7
4. XTOXLINE, TI65	5
5. CancerLit, CL63	3
6. SOMED, SM78	2

Tab. 9: Ranking of databases in the third database pool – 21 commercially charging databases

Ranking of databases	Number of relevant documents
1. BIOSIS Previews, BA70	49
2. EMBASE, EM74	26
3. CAB Abstracts, CV72	14
4. ISTPB + ISTP/ISSHP, II78	11
5. SciSearch, IS74	11
6. MEDITEC, MT68	4
7. Elsevier BIOBASE, EB94	2

free access. Searching in this pool retrieved 253 documents, 117 documents were evaluated as relevant. Therefore, the number of retrieved relevant documents in commercial, charging databases was higher than in free–of-charge databases.

Ranking of search terms

We have drawn up a first ranking of search terms and databases for searching for articles on alternative methods for acute oral toxicity testing based on the total number of relevant documents retrieved (see tab. 4-6).

Tables 4 and 5 show that the search terms “alternativ?” and “procedure?” provided the most relevant documents in free-of-charge databases. Search terms “alternativ?” and “method?” retrieved the most relevant documents in commercial, charging databases. Search terms “alternativ?”, “procedure?”, and “method?” retrieved more relevant documents than the term “vitro” in all database pools.

Ranking of databases

The number of total relevant documents was determined in relation to the search query as well as in relation to each database used in our study. These numbers provide a ranking of the databases (see tab. 7-9).

Six of 23 free-access databases can be recommended for searching for alternative methods for acute oral toxicity testing. These are MEDLINE, MEDLINE Alert, AnimAlt-ZEBET, XTOXLINE, Cancerlit and SOMED.

In addition, 7 of 21 commercial, charging databases can be recommended, i.e. BIOSIS Previews, EMBASE, CAB Abstracts, ISTPB + ISTP/ISSHP, SciSearch, MEDITEC, and Elsevier BIOBASE. Searching in these databases retrieved quantitatively more relevant documents than searching the databases that do not charge for use.

Discussion and conclusion

Our study has evaluated a step-by-step procedure for searching for documents on the topic of acute oral toxicity testing. We carefully selected databases and search terms based on our own AnimAlt-ZEBET database and the internationally accepted MeSH Thesaurus. The relevance of the retrieved documents was evaluated by scientists in comparison with documents and literature from AnimAlt-ZEBET. The results were summarised in a ranked order of search terms and databases.

It became evident that it is useful to start searching with broad search term phrases. Ranking of terms for the next steps of searching differs between databases that do charge for access or do not charge. For example, searching in free-of-charge databases using the terms “alternativ?” and “procedure?” can be recommended. In comparison, the terms “alternativ?” and “method?” can be recommended for commercial, charging databases.

Search terms “alternativ?”, “procedure?” as well as “method?” retrieved more relevant documents on alternative methods to acute oral toxicity testing than the term “*vitro*” in all databases. This result confirms that most alternative methods for testing acute oral toxicity still use animals. Although alternative methods may require the use of animals, the numbers of animals needed for any of the alternatives are drastically reduced. Moreover, one of the alternative tests does not require the death of animals as an endpoint (OECD, 2002).

The database ranking confirmed that MEDLINE is the first choice for searching on the topic of acute oral toxicity testing in databases that do not charge. However, the other ranked databases should be included in searching, because these databases cover a different spectrum of literature and therefore compliment each other. Furthermore, databases that charge for access, such as BIOSIS and EMASE, significantly improve information searching. Each of these databases has its own profile and contains relevant references not available in the other.

Our pilot study focused on one topic, acute oral toxicity testing, and was limited to general terms describing alternatives. We did not search for a specific method, such as the acute toxic class method. We searched very broadly and therefore remained only on the surface of this topic. However, as always, our recommendations offer a well-proven lead-in to searching.

Further investigations are necessary and should be extended to

other topics, e.g. production of monoclonal antibodies or food hygiene. Also, studies in the Internet with search engines such as Google.Scholar or Scirus (Elsevier) would be important. In addition, collaboration is needed among information specialists for alternative methods to develop standard terminology and standard protocols for searching strategy recommendations.

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The Animal Welfare Information Center: Helping the Community Meet the Information Requirement of the Three Rs

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Summary
The following paper presents a brief overview of the legal requirement of the U.S. Animal Welfare Act regarding the search for alternatives. The establishment of the Animal Welfare Information Center at USDA's National Agricultural Library is described. The AWIC approach to searching bibliographic databases for the 3Rs is outlined and examples of the approach, terminology, database choices, and the development of the search strategy are defined and illustrated. A sample search for alternatives in training protocols for trauma life support is provided and discussed.

Keywords: USDA's Animal Welfare Information Center, information services, US Animal Welfare Act, searching the literature for the 3Rs

Introduction

More that 15 years ago, the Animal Welfare Information Center (AWIC) of USDA's National Agricultural Library (NAL) provided time, enthusiasm and monetary support for "The World Congress on Alternatives and Animal Use in the Life Sciences: Education, Research, Testing". The Congress took place on November 14-19, 1993 in Baltimore, Maryland, USA. Obviously, there was and still continues to be enthusiasm for international dialogue on the important topic of how animals are used in education, research and testing.

For 19 years, AWIC staff has worked hard to meet the Congressional mandate to collect and produce a variety of information products, refine searching approaches, and to share knowledge regarding animal care, environmental enrichment and the "alternative search". Today's presentation will cover three basic topics: 1) a very brief overview of the U.S. Animal Welfare Act (U.S. Government Printing Office, 1985) requirements as related to alternatives; 2) A brief overview of the Animal Welfare Information Center; and 3) the AWIC approach to searching literature and other resources for alternatives.

The US Animal Welfare Act (AWA)

The first Laboratory Animal Welfare Act, U.S. Public Law 89-544, was enacted in 1966 with the purpose of preventing pet dogs from being stolen and ending up being used in biomedical research. The law granted the regulatory authority to the Department of Agriculture (The Animal and Plant Health Inspection Service, Animal Care (APHIS, AC)) where a programme was developed to write the regulations to interpret the Act and set up a nationwide inspection system.

In the third amendment in 1985, sweeping changes were made in the law. It provided more protection to animals in research, to exhibition animals and pets, considered humane transport and added more protection of owners from pet theft (U.S. Government Printing Office, 1985) In this presentation the three new mandates relevant to this presentation are: 1) the role of the Institutional Animal Care and Use Committee (IACUC) and the review of research protocols for four animal use concerns; 2) the need for reviews of the scientific literature to prevent unintended duplication, reduce animal pain and distress, and to use improved methodologies; 3) the establishment of an information service at the National Agricultural Library (NAL) to help the regulated community meet information requirements/needs. The service is the Animal Welfare Information Center programme.

Animals covered. The US AWA includes all warm blooded vertebrates with the following exclusions: 1) *Rattus* and *Mus* species; 2) birds bred for research; 3) farm animals used in agricultural research and teaching; 4) horses not used in biomedical research (i.e. rodeos, racing, pony rides, etc.); and 5) retail pet trade except for exotic species and pocket pets.

Activities regulated. Activities regulated under the AWA include the following: animal breeders and dealers, animals used in biomedical research and testing, higher education, in transport situations, and in exhibits (zoos, circuses, and marine mammals).

Alternatives search mandates. The AWA mandates principal investigators (PIs) to consider and document their process for the consideration of "alternatives" "to any procedure that would reasonably be expected to cause more than slight or momentary pain or distress in a human being". PIs are also required to write an assurance statement that an alternatives search or a consulta-

tion with a recognised expert was done for the protocol. The written assurance statement is to include the following: 1) consideration of alternatives based on the 3Rs of Russell and Burch (1959); 2) sources consulted; and 3) databases searched with names, search date and time period covered, keywords and/or search strategy used. The requirements are detailed in Policy # 12 of the APHIS, AC policy manual. (http://www.aphis.usda.gov/ac/policy/policy12pdf.)

The IACUC is responsible for reviewing all institutional protocols that use live animals to ensure the four following concerns are addressed: 1) painful or distressful procedures performed with analgesics or anaesthetics; 2) the research animal is used for only one major operative procedure unless justified; 3) ensure the PI has explored alternatives to painful or distressing procedures; 4) review the PI's written assurance that the research is not unnecessarily duplicative.

The Animal Welfare Information Center (AWIC)

Congressional mandates for AWIC. The US Congress directs the AWIC programme to provide information on the following topics: 1) information that can be used to train employees to use animals appropriately and treat them humanely; 2) aid in providing information that can prevent unintended duplication of research; 3) information that supports the various intents and requirements of the Animal Welfare Act; and 4) improved methodologies of experimentation that reduce animal use, minimise pain and distress, and are less invasive and distressful to the animals.

Services and information products offered by AWIC. In the 19 years since the Center was established, it has provided a variety of services and information products: reference services that include the alternatives search, training via workshops, presentations and exhibiting at conferences, authoring articles, and producing many types of topical publications within the Congressional mandate.

AWIC's user community. Those regulated under the AWA make up 50% of the user community. Other users include local, state and federal government officials; educators; students; libraries; organisations; the media; and the general public. AWIC staff also provide information to researchers around the globe. The following statistics give the reader some idea of the Center's usage. In the last 10 months, the Center responded to ~2,000 reference requests, distributed >25,000 information products, exhibited at 10 meetings, and conducted 15 formal training events.

The AWIC website. Most information products/materials produced during the 19 years have been converted to HTML documents and are available on the AWIC Website <http://www.nal.usda.gov/awic/>. It is a large Website with thousands of pages of content and carefully selected links. Briefly, the Website contains resources that address lab animals, farm animals, animals in exhibits and wildlife, and companion animals. Topics covered include laws and regulations, various techniques and methods, animal diseases, animal models of disease, animal care, addressing pain and distress, environmental enrichment, species-specific information resources, database links, and the "alternative search". From October 2004 to July 2005, there were 2,239,485 hits and 261,729, 248 kBytes were sent. Many users are from outside the US.

Searching for alternatives: The AWIC approach

Reasons for searching for alternatives

In addition to the legal requirements, there are certainly many persuasive reasons for trying to find alternatives to the use of animals in painful procedures. 1) For example, to gain AALAC International accreditation, an institution needs to follow the laws of the "Guide for the Care and Use of Animals". 2) There are societal pressures to make research and testing more pain and distress free by moving to lower species of animals or using no animals at all. 3) There are humane reasons based on ethical concerns about how animals are used and whether they should be granted "rights". 4) There are economic reasons, as animal-based research is expensive, i.e. the costs of: the animals, the facility requirements, the equipment including caging, cleaning and maintenance, feed, and specialised personnel. 5) Science-based reasons are also compelling and are addressed separately below.

At least nine scientific reasons that come rather quickly to mind. 1) Importantly, to perform up-to-date research, a PI needs to stay current in his/her research area. Obviously then, the search should be done *before* a new protocol is written. 2) A good search will address the duplicative research question. 3) Selection of a broad spectrum of databases will allow for a check of unusual sources. 4) The likelihood of using the appropriate numbers of animals increases. 5) We have seen people find new insights leading to new approaches for their research, possibly revealing methods of using other animals and non-animal models. 6) If caretakers and veterinarians understand the physiology, proper handling, training, enrichment possibilities, instinctive behaviour, etc., the animals will be better research subjects. 7) Researching the compounds in a protocol will reveal whether the compounds are appropriate or whether there are confounding factors in the protocol. 8) There is the potential to use less painful and invasive procedures, which leads to better data. 9) The search may reveal that collaborations at institutional, national and international levels may lead to better research and more efficient use of animal, human, facility and monetary resources.

Building blocks for a search

Two important building blocks used to interpret the concepts and realities of the protocol to construct an effective literature search are 1) terminology and 2) information resources.

Terminology – general

Considerations of terminology should include but not be limited to protocol concepts, the general area of study, compounds, techniques, equipment, scientific terms, terms relevant to the 3Rs, Boolean logic operators, limit terms, document types, etc. The fol-

lowing examples will hopefully be useful in understanding the terminology-based decisions needed. Note that in the examples below, "like terms" are put together and the "?" indicates truncation of the word to allow variations in the word endings. (The author recognises the "?" is not used universally in database platforms.)

- Examples: hypothesis related (cardiac surgery); generic and trade names (xylazine, rompun); acronyms (BSE, cns, mab); synonyms (kuru, prion?, scrapie,); truncation examples (pig? stud?). Spelling is a critical concern as databases contain information in various spellings: American (estrous, estrus, labor) and English (oestrous, colour, labour). Variations in words need to be thought about (tse, transmissible spongiform encephalopathies). Those annoying abrv.'s (abbreviations) can make life difficult. Many taxonomic names are in Latin and if there has been revision in the taxonomic name of an organism, the searcher will need to use the new and the old names.

Terminology – alternatives related

The terminology for this part of the search consists of examples of terms that address reduction and refinement as well as a set of terms that address replacement.

- Examples of reduction and refinement might include the following: analges? or painkiller or anodyne; anesthe? or anasthe? or anaesthe?; technique? or method(s) or procedur?; monitor? device? or evaluat?; restrain? or immobili? or restraint? or restrict?; advers?; positive reinforce? or animal training. Note: Most terms used here are developed from the area of study in the protocol!
- Examples of replacement terminology might include the following: model? or artificial, or *vitro*, or culture?; insect? or invertebrate? or fish, or cephalopod?; simulat?, or digital, or interact? or virtual or mannequin? or manikin or model, or assay(s); tissue? or organ? Note: there are numerous places to find possible alternative terms, but the Indexing Branch of the National Agricultural Library that produces the database AGRICOLA has also developed a mini-thesaurus of alternative-oriented terminology. It is called the Animal Use Alternatives Thesaurus. The mini-thesaurus can be used both for retrieval as well as for assigning keywords to an article. Look for this specialised thesaurus under the "Literature and Databases" section of the AWIC website.

Terminology – Boolean and other

There are 3 Boolean logic terms used for sophisticated database retrieval. They are OR, AND and NOT. "OR" tells the system to try and retrieve citations that have at least one of the words in the search statement. "AND" directs the database system to select citations that contain both terms connected by the "AND". "NOT" will eliminate a term or a group of terms from the possible retrieved items.

Other terms can be used to define from which fields the terms should be retrieved. For example, you can limit the retrieval to only the title field (ti), the descriptors (de), or the identifier (id). In the example note application of the topics discussed above. The "S" below stands for select in the DIALOG system.

? Truncation
  --S behav? = behave, behaves, behaviour, behavior, etc.
OR Select all citations with at least ONE word in the set
  --S swine or pig or pigs or porcine
AND Select all citations containing both words
  --S swine and euthan?
NOT Eliminates a term or group
  --S (pig or swine or porcine) not guinea
TI, DE, ID Limit term/s to title, descriptors, or identifiers.
  --S (dog or dogs or cani?)/ti, de, id

Searchable Information resources

The decision on where to retrieve information is critical! Many people do not know how much content varies between databases! When choosing a database resource, be aware of the subject coverage, years of coverage, selection criteria for inclusion, types of materials indexed (i.e. journal, books, reports, conference proceeding, patents, editorial comments, etc.) to build the resource. Such information is usually quite easily found, but requires some research. For example, MEDLINE and the European biomedical database EMBASE are very biomedically oriented. Citations are selected from 4-5000 journals. AGRICOLA, CAB, BIOSIS, and many other databases select from a broader base of resources – books, conference proceedings, reports, electronic resources, government reports, etc. and have a broader subject coverage. Note that such information is also useful for authors wanting a better idea of which database(s) index which resources.

Formulating a database search

The following illustrates the application of all the information given above as building blocks to answer a request often received at AWIC. Note: Refer to Jensen (2005) "Worksheet and Instructions for Alternatives Literature Searching." (This search was developed for attendees to the AWIC workshop.) The worksheet can be viewed under the "Literature Searching and Databases" section of the AWIC website.

An interested person (Dr. Breager) teaches an advanced trauma life support course at a medical school. He uses live pigs and dogs. The animals are euthanised at the end of the course. Although this has been the standard approach, Dr. Breager would like to know if there are any non-animal models or other alternatives.

Using the refined two-step approach, AWIC staff selects terms that would reduce and refine first, and terms for possible replacements last. Then terms are organised into a search strategy using all the information about searching presented above. Appropriate databases are chosen and the strategy is executed.

Databases selected

The databases are chosen because they have medical or veterinary resources, and technology citations from national and international sources. There is no limit to the years covered.

AGRICOLA	file 10
MEDLINE	file 155
NTIS	file 6
FEDRIP	file 266
BIOSIS	file 5
PASCAL	file 144
EMBASE	file 73
INSPEC	file 2

EI COMPENDEX file 8
JAPANESE SCIENCE AND TECHNOLOGY file 94

Search strategy
The results of the search strategy developed for Breager and executed in the above databases are as follows (tab. 1). Note: Sets 1, 2 and 3 contain terms and logic operators to retrieve citations that potentially offer reduction or refinement. S4 terminology is to retrieve replacement information. "RD" means duplicates were removed. In S6, the citations retrieved are to be limited to those with terms in the title, descriptor and identifier fields.

Some of the titles of citations retrieved:
Animal models
- Use of the ferret as a model for pediatric endotracheal intubation training. (file 10)
- Swine and dynamic ultrasound models for trauma ultrasound testing of surgical residents. (file 155)
- Ocular trauma modeling (file 73)
- Ultrasound training during ATLS: An early start for surgical interns. (file 5)
- *Battlefield Biomedical Technologies* (file 2)
- Removal of corneal foreign bodies: an instructional model (file 144)

Non-animal models
- Practicing procedures on the recently dead. (file 155)
- Virtual reality, robotics, and other wizardry in 21st century trauma care. (file 155)
- Paediatric resuscitation manikins. (file 155)
- Animal cadaveric models for advanced trauma life support training. (file 155)
- "Full scale" simulation in practical emergency medicine conception as represented by the Wurzburg anaesthesia and emergency medicine simulator. (file 73)
- MEDSIMM: Computer-simulated training for pediatric advanced life support (a work in progress). (file 5)
- *Medical Simulation for Trauma Management*. (file 6)
- *Enhanced Training using the Life Support for Trauma and Transport*. (file 144)
- Simulation and modeling of penetrating wounds from small arms. (file 2)

From the sampling of the results above, it seems likely that Dr. Breager will certainly have the opportunity to totally revise his training protocol! In fact it was interesting that a recent National Public Radio programme reported that a major university in the New York City area has completely changed their trauma training to non-animal technologies.

One last part of the process that should be addressed is the review of a search such as that above. If you are in the position of reviewer, look carefully at the following: the databases chosen, how the terms were selected and used, and how the Boolean logic was applied. If you do not perform each stage correctly, you can very easily come up with no information. A word of caution, if one does not perform each of the stages of the alternative search with intelligence and care, you can easily have zero hits returned. With the incredible volume of scientific information that has been carefully place in searchable database, zero hits are possibly a disservice to the scientific community and to the research animals.

The author hopes that the information included in this paper will provide information, knowledge, approaches, tips and tricks to formulate and execute an adequate and productive search for the 3Rs.

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Tab. 1: Results of the search strategy

Set	Term Searched	Items
S1	trauma or life(w)support or emergenc?(1n)medic? or ems or emst or atls or advanced(w)trauma(w)life(w)support	440 688
S2	train? or teach? or educat? or instruct? or tutor?	2 118 835
S3	dog or dogs or canine? or pig or pigs or swine or piglet? or ferret? or cat or cats or animal or animals	2 419 446
S4	alternative? or model? or simulat? or cadav? or carcas? or software or video? or interact? or digital? or virtual or mannequin? or manikin? or computer?	16 081 397
S5	(s1 (4N) s2) and s3	621
S6	RD (unique items)	574
S7	(s1 and s2 and s4)/ti,de,id	1 387
S8	RD (unique items)	1 150

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Considering Animal Alternatives and Welfare *via* a Comprehensive Search of the Scientific Literature

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Summary
Searching the bibliographic databases for alternatives for the use of animals in research, teaching or testing, and considering alternatives to potentially painful or stressful procedures are regulatory requirements common to the US and member states of the EU, as well as several other countries. Effective searches are those completed in a variety of databases using a sophisticated and well considered strategy. Efficient searches are facilitated by the development and use of new search grids, practically organised by type of research, proposed animal model and research topic.

Keywords: alternatives, animal welfare, compliance, database

Introduction

The search for alternatives to comply with the related animal welfare regulations might seem to be a straightforward endeavour, yet resistance and scepticism continue from many scientists. Considering the Three Rs (replacement, reduction and refinement) and thus alternative experimental methods is now required by legislation in many countries. In the United States, the alternatives search requirement is included in the Animal Welfare Act in order to assure the general public that no animal used in research, teaching or testing will experience unnecessary pain or distress (United States Animal Welfare Act, 2002). In Australia, New Zealand and in the member states of the European Union, legislation requires that scientists provide evidence that the use of animals is justified and that they assess whether less stressful or painful procedures are available (Wood, 2005). While simply meeting the requirements for compliance is not difficult (a list of databases searched, the dates searched, the search terms used, and a discussion of what was found), giving thoughtful consideration to the breadth of alternatives and actually locating relevant information is uncommon. However, if a comprehensive search is performed, by searching all of the scientific literature published in a specific area of study, the information retrieved will be much more relevant, and proper attention to animal welfare is assured.

In order to identify and consider potential new methods and procedures, it is necessary to regularly search the published literature. Improved research methods may suggest alternative procedures that can reduce pain or distress, or even replace animal experiments. Already familiar with locating scientific material for their research, scientists can readily learn to expand their literature searches to include additional databases. At the same time, the concept of alternatives and the Three Rs objectives can be more clearly defined and explored. Expanding the search to include new ideas and technologies, as well as aspects of husbandry and care such as housing, blood collection, analgesia, anaesthesia and humane endpoints, will improve the utility of the results and facilitate compliance. New web-based resources located at the UC Center for Animal Alternatives main website, http://www.vetmed.ucdavis.edu/Animal_Alternatives/main.htm (Wood et al., 2005a) are designed to assist with a comprehensive search and to prompt the user to identify and consider additional concepts and databases.

Guide to Bibliographic Databases for Alternatives Searching

Scientists may locate information on their research, as well as on alternatives, in a variety of formats and systems, including printed and online bibliographic databases, specialised services and information managers and organisational and societal websites and resources. Even with so many useful options, the most common path to compliance is to search in a single database: PubMed. While this approach is clear-cut, identifying useful and relevant information is not a simple task. The principal barrier to effective searching and meaningful compliance is the misunderstanding of bibliographic searching (Grune, 2004). Together with an inconsistent interpretation of the Three Rs, searching for and locating quality information is a challenge. Each bibliographic database indexes a unique set of journals, but too often researchers use databases that do not cover their specific topics. Starting with an appropriate database that covers the type of information being sought is a first essential step towards conducting an effective search that can yield useful information to enhance animal welfare (Hart, 2005). In order to help researchers assess which databases may be appropriate when searching for particular types of information, we have developed a new web-based resource: *Guide to Bibliographic Databases for Alternatives Searching: Database Approach to a*

Search (Wood et al., 2005b). It is a simply presented grid arranged by both Animal Models and Topics. It includes live links to free databases that are accessible from around the world, including PubMed, AGRICOLA, PrimateLit, FishBase, TOXNET, ILAR Animal Models and others. Proprietary databases are listed as well, providing live links for affiliates to the University of California holdings. While only available to those with subscriptions, the listing of proprietary databases acts as an educational tool by increasing awareness of specific database availability. These are also arranged by Animal Model and Topic, and include PsycInfo, Zoological Record, Web of Science, BIOSIS, CAB and others. Depending on the institutional contract, scientists may be able to download articles in full-text.

Grids arranged by animal models and topics

This web-based *Guide to Bibliographic Databases* assists both scientists and members of animal care and use committees in determining whether a particular selected database is reasonable. It also works to inform on the availability of additional potentially worthwhile databases.

The list of journals indexed in any database is limited, and some journal titles are only indexed selectively. Published scientific information is so vast that each database must identify its niche and focus on a specialised area. The use of animals in science is such that it crosses a variety of research areas, and the Three Rs, especially, must be considered from many perspectives. Biomedical scientists commonly assume that the PubMed database is exhaustive, indexing every relevant scientific journal, cover to cover. While extensive, PubMed is not all-inclusive. The collection of journals in PubMed is oriented primarily on biomedical research and does not address the veterinary and animal science journals well, for example. A scientist proposing to use a bird or fish model may miss most of the published literature if PubMed is the only database searched; other databases to consider include BIOSIS and Aquatic Sciences and Fisheries Abstracts. AGRICOLA is an excellent database for animal science and veterinary literature, but focuses on US publications; CAB, with its European coverage, should also be searched to ensure broad consideration of this topic. Searching in multiple databases allows retrieval of different sources of information in order to realise a more comprehensive search.

Effective consideration of the Three Rs also requires using detailed search concepts, from specific research areas such as toxicity, tumour models and disease studies to more general issues such as analgesia, endpoints, imaging and euthanasia. By using the appropriate terms and resources, particularly useful material may be found, providing information that is otherwise very difficult to isolate. The grids in the *Guide to Bibliographic Databases* list common reoccurring topics, while providing links to specific resources, including books, bibliographies and specialised databases. For example, AWI Comfortable Quarters is valuable for housing questions, ILAR and AltWeb provide access to elusive information on humane endpoints, and ANZCCART Fact Sheets publish useful and very practical information on such things as managing laboratory animal pain. Topics such as blood collection, husbandry, identification, and behaviour, critical to the implementation of the Three Rs, are also topics that are frequently overlooked. Specialised publications and indexes, resources created by organisations and associations, have proven very valuable in the comprehensive search for alternatives.

Responsible literature searching

When animal welfare legislation requires the researcher and animal care oversight committees to consider alternatives and the Three Rs, a comprehensive and thorough alternatives search is expected. Supporting scientists' efforts in this area, and as part of a larger effort, a concise table of available databases and resources was recently developed, titled *Responsible Literature Searching* (Wood et al., 2005c). Organised by headings, "Research, Teaching and Testing," informational resources are listed and linked. The table is further divided into three sections: "Free Bibliographic Resources, Proprietary Bibliographic Databases and Free Governmental, Regulatory, and Organisational Databases". For each database, there is also a link to additional information about that database, allowing the user to learn more about the resource in order to determine whether it may be of relevance and should be included in the search.

If one is searching in the toxicology and testing area, there are several databases listed under the free databases section (i.e. Toxnet, EPA-EcoTox), a couple more listed as proprietary databases (i.e. ASFA and RTECS) and several more free resources under governmental, regulatory and organisational databases (i.e., ICCVAM, ECVAM, INVITTOX).

Similarly, under the topic of teaching resources, the user is provided with links to free databases, such as NORINA and AVAR, and to subscription-based databases, such as ERIC, CAB, and Zoological Record. At any time, the associated link will provide access to additional information on that particular resource, including its relevance to the proposed search.

Conclusions

The amount of scientific information currently being published and made available is overwhelming. If scientists are to thoroughly understand a proposed research study, or reliably decide on one method over another, they need help in managing the information. Their hope of finding just what they want when they need it requires some organisational assistance. The resources discussed here and found on the *UC Center for Animal Alternatives* website will help with that endeavour.

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