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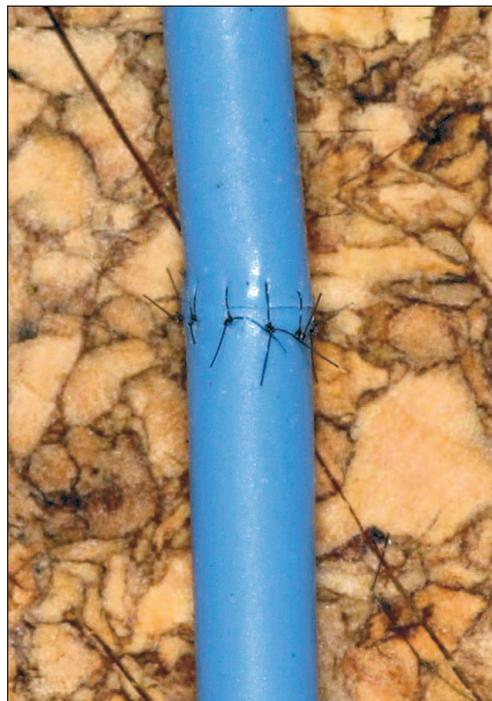
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Report and Recommendations of the International Workshop "Retrieval Approaches for Information on Alternative Methods to Animal Experiments"

held in Berlin in 2003 at ZEBET, Centre for Documentation and Evaluation of Alternative Methods to Animal Experiments, in the BfR, the German Federal Institute for Risk Assessment

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Summary

In the member states of the EU and in the USA, scientists are obliged by animal welfare legislation not to conduct an animal experiment if another scientifically satisfactory method is reasonably and practicably available. To meet the regulatory obligation to use alternatives to animal experiments, scientists should consult literature and other relevant sources on alternatives prior to any experimental study on laboratory animals. It is the responsibility of the individual 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 3 Rs concept of Russell and Burch (1959)).

Specialised information services provide support to scientists searching for publications on alternative methods. On occasion of a workshop in Berlin in November 2003, representatives of animal welfare information centres discussed currently available information sources on alternative methods, index terms for alternative methods, and search strategies based on index terms for alternative methods. ZEBET presented an investigation on the current status of indexing systems on alternative methods in established literature databases. The project analysed how the results of a search for publications on alternatives was influenced by the indexing procedure. The results of the study were exemplified by a typical search result. The results of the study indicated that the current indexing systems do not provide the required

Zusammenfassung: Bericht und Empfehlungen des internationalen Workshops „Suchstrategien für Informationen über Alternativmethoden zu Tierversuchen“, der 2003 in Berlin bei ZEBET im BfR (Bundesinstitut für Risikobewertung) stattfand.

Auf der Grundlage der Vorschriften der Tierschutzgesetzgebung sind Wissenschaftler verpflichtet, die Unerlässlichkeit von Tierversuchsvorhaben zu prüfen. Ein Tierversuch darf nicht durchgeführt werden, wenn andere wissenschaftlich anerkannte Methoden zur Verfügung stehen. Zur Erfüllung dieser Verpflichtung recherchieren Wissenschaftler in Literaturdatenbanken und anderen relevanten Informationsquellen über Alternativmethoden. Dabei ist es dem Wissenschaftler selbst überlassen, die geeignetsten Datenbanken und Suchstrategien auszuwählen. Fachinformationsdienste bieten Unterstützung bei der Suche nach Alternativmethoden für Tierversuche an. Auf dem Berliner Workshop im November 2003, trafen sich die Vertreter verschiedener internationaler Informationsdienste für Tierschutzfragen und Alternativmethoden und diskutierten über das gegenwärtige Informationsangebot über Alternativmethoden, Indexierungsbegriffe für Alternativmethoden und Suchstrategien, die diese Begriffe verwenden. ZEBET stellte eine eigene Untersuchung über Indexierungssysteme von Alternativmethoden in etablierten Literaturdatenbanken vor. Die Studie befasste sich mit der Frage, wie Suchergebnisse zu Alternativmethoden in internationalen Datenbanken durch die Art und Weise der Indexierung von Publikationen beeinflusst



information, since not all of the relevant information is indexed under "alternative methods". The workshop participants developed recommendations for ad hoc working groups and research projects, e.g. development of suitable search strategies on alternative methods for scientists.

werden. Die Untersuchungsergebnisse wurden anhand einer Beispielrecherche vorgestellt. ZEBET kam dabei zu dem Schluss, dass die gegenwärtigen Indexierungssysteme nicht ausreichend alle relevanten Publikationen zu Alternativmethoden erfassen. Die Teilnehmer des Workshops entwickelten Themenvorschläge für Arbeitsgruppen und zukünftige Projekte, um die Entwicklung geeigneter Suchstrategien über Alternativmethoden zu verbessern.

Keywords: alternative methods, in vitro methods, database, information, publications, searching, retrieval, Internet, index terms, thesaurus, workshop, 3Rs concept, ZEBET, BfR

1 Introduction

In assuring public and regulatory authorities that animal research is both ethical and in compliance with the law, scientists and institutional review committees of the member states of the EU and of the USA must provide evidence that the use of animals is justified for each project under review. The overall concept of "alternatives" has emerged as the primary ethical framework to determine whether the use of experimental animals is required to achieve scientific objectives and whether less stressful or less painful procedures can be used as substitutes for those initially proposed. In particular, the 3Rs concept of Russell and Burch (1959), to refine, reduce and replace animal experiments, has proven very useful for scientists and review committees in evaluating alternatives to animal experiments.

Among the efforts to implement the 3Rs concept during the past decades, database retrieval approaches on alternative methods to animal experiments have become a key issue. In 1985, the Animal Welfare Information Center (AWIC) of the U.S. Department of Agriculture (USDA) was established as one of the first information centres on alternative methods. Information services, including the development of specialised databases and websites on alternative methods, were discussed critically during the 1980s. More recently the discussion has focused on the problem of information retrieval in the heterogeneous environment of the World Wide

Web. Adamczak and Nase (2002) emphasised that in the era of electronic networks, the problem lies not in dispersing the information but rather in finding the right information within an appropriate time frame.

In 1996, at the workshop "Current Status and Future Developments of Databases on Alternative Methods" organised by the European Centre for the Validation of Alternative Methods (ECVAM), specific issues were discussed that arise when searching for information on alternatives in bibliographic databases (Janusch et al., 1997). Problems identified included the variety of information sources, different types of alternatives, as well as different indexing systems used by individual databases. Furthermore, in many databases the contents of abstracts do not contain the information required to indicate that the article contains information on alternative methods. It was recommended to define a list of preferred terms to be used by bibliographic and factual databases to index publications covering alternative methods. At the 3rd World Congress on Alternatives and Animal Use in Life Science in 1999, the need for an easier and more successful approach to retrieve information on alternatives was stressed again (Janusch-Roi et al., 2000).

It became apparent at the 4th World Congress on Alternatives and Animal Use in the Life Sciences in 2002 that improvement of information services for alternative methods should not only include consideration of the content of databases and websites but also the

development of suitable retrieval methods. Representatives of European and U.S. American information centres decided to continue the discussion in order to improve information retrieval on alternative methods, including both practical proposals that may be applied immediately and long-term tasks for research projects (Libowitz, 2002).

On 2nd-5th November 2003, this discussion was continued at the Berlin Workshop hosted by the National German Centre for Documentation and Evaluation of Alternative Methods to Animal Experiments (ZEBET) at the BfR, the German Federal Institute for Risk Assessment in Berlin. The workshop "Retrieval Approaches for Alternative Methods to Animal Experiments" encouraged and supported the discussion on improving search strategies and indexing systems.

The governmental requirements and animal welfare legislation of the EU and the USA form the basis for information service systems supporting the search for alternative methods. Scientists are obliged not to conduct experiments on animals if another scientifically reliable method to obtain the desired information is available (Council Directive 86/609/EEC, United States Department of Agriculture, 1997 and 2000). In particular, consideration must be given to methods that either avoid animal experiments altogether or minimise pain and suffering of the animals or reduce the number of animals used. Scientists are generally required to consult literature and other relevant sources for alternatives prior to any experimental study using animals.



2 Information resources and search strategies

To meet the legal obligation to use alternatives to experimental animals, scientists have access to information on alternatives to animal studies via a variety of printed and online sources, including web-based bibliographic databases and specialised websites. Scientists expect to obtain accurate, complete and relevant information within a short time frame. Although it is ultimately the responsibility of each scientist to select the most appropriate database and search strategies depending on research goals and methods employed, the following general questions are also important:

- Are the available information resources sufficient to fulfil the demands of animal welfare legislation?
- Can the information be retrieved appropriately?

At the Berlin Workshop, representatives of animal welfare information centres discussed the information sources currently available, practical solutions as well as proposals for ad hoc working groups and further research projects. The workshop focused on information retrieval on alternative methods applied in biomedical research rather than in education and teaching.

2.1 ECVAM Scientific Information Service on advanced alternative methods to animal experiments in biomedical sciences – a project of the European Commission

<http://ecvam-sis.jrc.it>

The ECVAM Scientific Information Service (SIS) is part of ECVAM, which was established by a Communication of the European Commission and Parliament in 1991 in response to Directive 86/609/EEC on the protection of animals used for experimental and other scientific purposes (SEC(91)1794). Directive 86/609/EEC requires that the Commission and Member States should actively support the development, validation and acceptance of methods, which could reduce, refine or replace the use of laboratory animals and encourage research into the development and validation of alternative techniques.

SIS was established in 1996 to achieve one of the principal objectives of ECVAM required by the European Commission and Parliament, i.e. to establish, maintain and manage a database on alternative procedures to animal experimentation. SIS, therefore, provides scientific knowledge on the use of alternatives in biomedical sciences and serves Commission Services and national policy-makers, as well as scientists and the animal welfare movement. SIS is responsible for the SIS databases, the ECVAM thesaurus and the ECVAM website.

2.1.1 SIS Databases

<http://ecvam-sis.jrc.it>

The SIS databases provide factual and evaluated (ready-to-use) information on various aspects of advanced non-animal methods in the biomedical sciences. The focus is on toxicological methods at any stage of development and validation. Currently, the SIS databases cover 21 topics in the area of toxicity testing of chemical compounds with the following spectrum of information: methods (summary descriptions and/or protocols, such as the INVITTOX protocols), inter-laboratory evaluations, test results and formal validation studies.

The core application of SIS, the methods database, provides information on the rationale for method development, e.g. the scientific principle, special end-points and the test systems used for the data analysis and the status of development and/or validation. This information is based on extensive literature reviews. Currently, this sector covers 39 method summary descriptions and a collection of 130 protocols, the INVITTOX protocols, which provide step-by-step descriptions for each *in vitro* method.

Furthermore, 2479 references are currently stored in a database. To date there are 2500 registered SIS users from 65 countries in academia (41%), industry (34 %) or governmental (17%).

2.1.2 The ECVAM Thesaurus

In 1999, SIS started the ECVAM Thesaurus project. The ECVAM Thesaurus on Advanced Alternative Methods (TAAM) focuses on the creation of a systematically ordered collection of harmonised terms on animal alternatives

in the biomedical sciences. ECVAM SIS co-operates in this project with the Fund for the Replacement of Animals in Medical Experiments (FRAME, UK), ZEBET, and the National Library of Medicine (NLM, USA). A “bottom-up approach” was used to develop a thesaurus based on actual phrases in 2000 scientific documents. The first classification scheme contains 1000 unique terms.

In 2004, an open source list of the thesaurus will become available online to promote discussion among end-users. The follow-up will depend on the acceptance by the scientific community. The ECVAM Thesaurus is designed as a “tree structure”. Every term is sorted in a hierarchy containing approximately 11 main topics with individual identification numbers and individual “tree branch” numbers. The objective of the ECVAM Thesaurus is to improve the retrieval of information on animal alternatives in databases and is limited so far to the SIS databases.

2.1.3 The ECVAM website

In 2002, a new ECVAM website (<http://ecvam.jrc.it>) was established and made available on the Internet. It is designed to keep the customers and collaborators of ECVAM, as well as the general public updated on alternatives to testing in animals. The website provides details on in-house and external collaborative activities, in addition to general information about ECVAM. Information on validation studies carried out with the involvement of ECVAM is provided, including the list of validated methods and major ECVAM publications. The website also provides access to statements of the ECVAM Scientific Advisory Committee and cross-references to the online version of the ECVAM SIS databases.

Recently, registration facilities of the ECVAM mailing list were installed to provide external users with regular updates on ECVAM. Links are offered to international and federal organisations, e.g. the service of the European Commission services and to ICCVAM (Interagency Coordinating Committee on the Validation of Alternative Methods, USA).

Verifying and understanding user requirements has been a major emphasis of



the SIS databases since 2001. A new integrated Internet version of the SIS has been under development since 2001. It is designed to provide access to the entire information content of SIS. This new version is expected to come online in 2004. Furthermore, it is intended to provide an interactive training tool for validated methods and to extend the SIS databases by a section on *in silico* methods.

2.2 Altweb – the Internet clearinghouse on the 3Rs

<http://altweb.jhsph.edu>

In 1997 the Johns Hopkins Center for Alternatives to Animal Testing (CAAT, USA) launched Altweb, the Alternatives to Animal Testing Website. Altweb was created to serve as a central reference point for information on alternatives, publications, databases, itineraries, and other resources on the Internet.

Altweb is managed by CAAT on behalf of an international project team, which acts as the steering committee for the site. Currently, the project team includes representatives from 25 organisations in industry, academia, the animal welfare community, and government agencies from the United States, Canada, and Europe. Team participants include the Animal Welfare Information Center of the US Department of Agriculture (USDA), the US Food and Drug Administration, the Procter & Gamble Company, ECVAM and ZEBET.

Altweb serves multiple audiences from many backgrounds, including biomedical researchers, industry, the international alternatives community, the international regulatory community, authorities that review animal protocols, the animal welfare community, individuals and groups who work with laboratory animals (technicians, veterinarians, etc.), teachers, students, and the general public.

Resources available on the Altweb site include:

- a database on pain management (anesthesia and anaesthesia)
- a new database on humane endpoints
- abstracts from the major journals in the alternatives field
- relevant reports, proceedings, articles, and newsletters
- full-text of the classic Russell and Burch book, “Principles of Humane Experimental Technique”, and the book “Animals and Alternatives in Testing: History, Science, and Ethics”
- regular news updates in the alternatives field
- a calendar of meetings in the alternatives field
- a directory of funding sources for alternatives research
- links to websites from relevant organisations and institutions worldwide
- a list of acronyms commonly used by the international alternatives community
- a special section on alternatives to animals in monoclonal antibody production
- FAQs, or frequently asked questions, that address a broad range of alternatives-related issues
- a regulations page that provides links to important documents describing the laws, policies, and guidelines pertaining to animal care and use in the United States, various European countries, Australia, and New Zealand (future plans call for expanding this section to cover regulations from South American countries and other parts of the world as well)

Altweb usage has grown steadily over the last seven years. In 1998, Altweb’s first full year of existence, the site logged more than 80,000 users. Figures for 2003 show nearly half a million visitors over the course of the year. About two thirds of the users were from the United States; the other third represents some 120 countries around the world. The average user session time ranged from 12 minutes to more than 18 minutes in any given month – a considerable length of time in the fast-paced world of the Internet. These statistics indicate that Altweb provides much-needed information and is effectively serving as a searchable global information resource.

2.3 ALTBIB – NLM’s alternatives to animal testing database on the web

<http://toxnet.nlm.nih.gov/altbib.html>

In 1992, the Bibliography on Alternatives to the Use of Live Vertebrates

in Biomedical Research and Training (ALTBIB) was established as a part of the Specialised Information Services (SIS) Division of the NLM within the National Institute of Health (NIH), U.S. Department of Health & Human Services.

Currently, ALTBIB contains 7,595 relevant citations from 1992 to 2002 which were selected by searching PubMed and TOXLINE and which have been combined into one easily searchable database. The citations relate to methods, tests, assays and procedures that may prove useful in establishing alternatives to the use of animals.

ALTBIB offers special search features, for example:

- relevance ranking, i.e. references are sorted according to relevance
- chemical synonyms search
- MeSH (Medical Subject Headings) mapping, i.e. queries are based on MeSH terms, the controlled vocabulary of the NLM
- searching by category, i.e. queries can be limited to one of the following 15 categories: carcinogenesis, cytotoxicity, dermal toxicity, ecotoxicity, genotoxicity and mutagenesis, hepatic and renal toxicity, immunotoxicity, neurotoxicity, ocular toxicity, pharmacokinetic and mechanistic studies, pulmonary toxicity, quantitative structure activity relationships (QSAR), reproductive and developmental toxicity, tissue and organ toxicity, and miscellaneous
- searching by date
- searching by author

ALTBIB is embedded in the services of the NLM. Its future updates will be based on:

- a list of key journals, for example: “Toxicology”, “Toxicology *in vitro*”, and “Food and Chemical Toxicology” and
- a link to LocatorPlus (NLM’s online catalogue) to search for books at the NLM.

In the near future ALTBIB users will be able to automatically launch a search in PubMed, retrieving publications relevant to the 3Rs by using predefined strategies, which include key terms and MeSH terms.

2.4 AnimAlt-ZEBET – an Internet database on alternatives to animal experiments

<http://www.bfr.bund.de>

In 1989, the Centre for Documentation and Evaluation of Alternative Methods to Animal Experiments (ZEBET) at the German Federal Institute for Risk Assessment (BfR) was established to provide an information service and to create a database on alternative methods to animal experiments. ZEBET makes available its information primarily to scientific and animal welfare committees that regulate the use of laboratory animals at the state and community levels of the Federal Republic of Germany. ZEBET's information service is responding to inquiries from universities, individual scientists, the press, and the general public.

In 2000, ZEBET introduced AnimAlt-ZEBET, an Internet database on alternatives to animal experiments. AnimAlt-ZEBET can be accessed free of charge on the Internet via the German Institute for Medical Documentation and Information (DIMDI), the official host of biomedical databases within the German Federal Ministry of Health, <http://www.dimdi.de> (Grune et al., 2000). One of the special features of DIMDI is that searches in AnimAlt-ZEBET may be combined with searches in well-established databases such as MEDLINE.

AnimAlt-ZEBET is an English full-text database on alternative methods to animal experiments. It covers alternative methods in many fields of the biomedical sciences and related disciplines and also contains information extracted from approximately 800 scientific journals, books, monographs, guidelines, and congress proceedings. As of November 2003, AnimAlt-ZEBET contained 115 documents. Each document consists of several data fields, e.g. title of method, keywords, evaluation according to the 3Rs principle, abstract and bibliographic references. The number of references within these documents is approximately 6000. ZEBET's Activity Report shows an average of about 23,000 visits per annum (for the years 2000 to 2003).

The basic concept of AnimAlt-ZEBET is to provide documents that have been

evaluated by ZEBET's staff according to the 3Rs principle developed by Russell and Burch (1959). AnimAlt-ZEBET also provides an assessment of the current stage of development, validation and acceptance of a method for either scientific or regulatory purposes. Each AnimAlt-ZEBET document is characterised by specific keywords. ZEBET's index terms correspond to those of MeSH, the controlled vocabulary thesaurus of the NLM. However, ZEBET's list of terms is not a controlled thesaurus. In general, each document is indexed using "animal welfare", "animal experiments", and "animal testing alternative" as the first terms. These are followed by terms giving more specific technical details for each method.

2.5 The web-based animal research training programmes of the U.S. Department of Veterans Affairs (VA, USA)

<http://www.researchtraining.org>

In January 2001, the Office of Research and Development of the U.S. Department of Veterans Affairs (VA) opened a comprehensive website at <http://www.researchtraining.org> to support medical and scientific institutions with training mandates. The VA intends to intensify training in animal science topics. Its web courses and exams are freely accessible 24 hours a day at home or at work and the web server keeps records and training documents to minimise local administrative burden. The animal research courses were developed in collaboration with the U.S. Office for Laboratory Animal Welfare (OLAW, USA) and the American Association for Laboratory Animal Science (AALAS, USA).

Currently, the VA web-based training programmes contain lessons for research staff and members of the Institutional Animal Care and Use Committees (IACUC, USA). Self-exams are available to document compliance with mandatory training requirements. Research staff can access a comprehensive course entitled "Working with the IACUC", and species-specific courses are also available. The VA also offers a comprehensive course for IACUC members entitled "Essentials for IACUC Members."

In May 2004, the VA site had over 27,000 registered users on its training website, with over 20,000 passed exams. Currently, the VA is working on the following projects:

- "Searching for Alternatives: Value, Use and Interpretation of Results": a course and exam to educate researchers on database searches for alternatives, produced in collaboration with the Animal Welfare Information Center (USDA AWIC, USA) and OLAW.
- "Justifying Animal Use: Application and Use of Statistical Concepts": a course and exam to educate researchers on power analyses, including the use of an online animal research statistics calculator, produced in collaboration with the OLAW. An online power analysis calculator specifically designed for animal research will be created as part of this initiative.

The course on database searches will cover three main topics: 1. search for alternatives, 2. additional benefits of a database search for alternatives and 3. using Boolean logic. The goals of this course are to explain the legal and ethical mandates for database searches for alternative methods, to help investigators perform more effective database searches for alternatives, and to help IACUC members evaluate database searches for alternatives during protocol review. At first, the fundamental principles of U.S. Animal Welfare Regulation and Public Health Service Policy are examined in detail (United States Department of Agriculture, 1997 and 2000). The quotations are linked to the original documents in text or PDF format. Furthermore, the principles of using Boolean logic are explained. To perform effective database searches, an investigator must have an understanding of Boolean logic ("OR", "AND", and "NOT" functions), which is utilised by software to detect the requested information in a database.

The course on statistical analysis is designed for:

- investigators to learn to use the web-based power analysis calculator developed specifically for animal research,
- investigators and staff responsible for



completing IACUC protocol forms with a need to understand how to properly use statistical concepts to justify animal use, and

- IACUC members who must evaluate justifications for animal use by employing statistical concepts.

For example, the course covers parametric and non-parametric tests, censored data, interpretation of p values, paired and unpaired data, type 1 and type 2 errors, and the meaning and use of power calculations in experiments.

2.6 The "Literature Search for Alternatives Worksheet" of the Animal Welfare Information Center (AWIC, USA)

<http://www.nal.usda.gov/awic/alternatives/searches/worksheet.htm>

AWIC is part of the USDA's National Agricultural Library (NAL) in Beltsville, Maryland, U.S. The centre was established in 1986 as mandated by Congress in the 1985 amendments to the Animal Welfare Act (AWA) to serve the information requirements and needs regulated under the AWA, e.g. using animals in painful procedures for biomedical research, product testing, higher education, zoos, circuses and marine mammals in aquaria. The focus of the centre's information products, services and activities is to help the regulated community address the 3Rs of Russell and Burch. The information provided by the centre is also directed at "refinement" via anaesthetics, analgesics, and improved methodologies.

The NAL also produces the bibliographic database AGRICOLA. Literature dealing with animal welfare issues and related topics is indexed for AGRICOLA in support of the AWIC program.

The AWIC staff has developed the "Literature Search for Alternatives Worksheet" to support scientists in conducting a search for alternatives. This worksheet was designed as an aid to researchers, information specialists, and IACUC members, as they begin to develop a multi-database search algorithm to determine whether alternative methods exist and to avoid duplication of previous research. The worksheet is based on many years of experience of the AWIC staff in conducting literature searches,

especially in selecting and combining keywords to search multiple databases simultaneously (Allen, 1997). Information and advice on this subject is contained in explanatory notes and recommendations for every step outlined in the worksheet.

The worksheet is divided into two parts. The first part addresses details of the planned investigations to develop a search strategy and run a multi-database literature search. It contains 12 data fields to be completed. In addition a search summary and three sample search algorithms are given.

The worksheet starts by identifying who the investigator is. Next, information on the area of study, proposed animal study, proposed animal species, protocol objectives and endpoints is asked. A list of keywords and a selection of databases is prepared based on this information. The actual search strategy consists of a reduction and refinement search and a replacement search using the selected keywords and databases. For example, the replacement search should include keywords for potential alternatives such as "vitro", "culture", or "simulation". The worksheet recommends a minimum of at least two databases to secure access to most of the relevant available information. The years of publication covered are also recorded on the worksheet so that the search can be updated periodically.

At the end of the worksheet an Alternative Search Summary is requested. The researcher should explain in short form the search profile and the search results.

Furthermore, the AWIC provides three sample literature searches for alternatives to explain how to structure a search.

The AWIC Literature Search for Alternatives Worksheet works like a checklist, helping to ensure that the requirements of animal welfare legislation are met and to prove the necessity of performing the scientific experiments using animals.

2.7 The Search for alternatives website of the UCCAA

http://www.vetmed.ucdavis.edu/Animal_Alternatives/main.htm

The UC Center for Animal Alternatives (UCCAA) acts as a co-ordinating office for the University of California (UC) on improved and alternative methods. UCCAA has a central mission to support scientists in gaining convenient access to alternative methods. In addition, the centre places special emphasis on disseminating information concerning models, computer programmes, and other animal alternatives in education. The UCCAA librarian serves the nine campuses of the UC. Studies at the UC range from applied biomedical research to exploratory biology, and species used include rodents, companion animals, farm animals, primates, marine mammals, and reptiles. Each particular campus has a unique context that affects the methods and types of protocols that shape their need for bibliographic searches for alternatives (Hart et al., 2000). The campus programmes include undergraduate studies, graduate research, and medical and veterinary education.

Tab. 1: Use of the UCCAA web resources; estimated daily use based on 28-day rolling averages from July 2000 through March 2004

Date	Number of users (daily average)
July - December 2000	27
January - June 2001	53
July - December 2001	66
January - June 2002	106
July - December 2002	133
January - June 2003	239
July - December 2003	318
January - February 2004	795
March 2004	928

The AWA and federal regulatory authorities, such as the USDA, and expert bodies such as the Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) require laboratories and research facilities to maintain a high level of involvement with animal care. The UCCAA supports the scientists in this effort by making information on alternatives to animal experiments more easily accessible via the Internet.

As indicated by the data in Table 1, the use of the UCCAA web resources has increased dramatically, especially over the past year. Such statistics provide evidence that research scientists are in search of timely, relevant information, and, as a result, are visiting this website.

Currently, the UCCAA website is divided into several main topics, which are then further divided into relevant sub-topics. The following are most relevant to the scientists' search for information on alternative methods:

- Comprehensive Search Strategies for Animal Research Protocols
- Alternatives in Education

2.7.1 Comprehensive search strategies for animal research protocols

The layout and search topics of these eight search grids are based on the eight AALAS tutorials "Preparing an Animal Protocol for Research", <http://www.aalaslearninglibrary.org/courses.asp?strKeyID=2532077318075438162940>.

This approach is based on the premise that scientists commonly work according to guidelines, with the ultimate goal of completing and submitting a protocol that is readily approved. The search grids combine research topics with search templates, using a variety of databases and/or websites. The research topic itself is divided into relevant sub-topics, which should then be checked for animal welfare legislation as well as the 3Rs; for example, a study protocol using animals must consider analgesics, sedatives, and anaesthetics. The search grid connects the concepts "anaesthesia" and "analgesia" with an embedded search in AGRICOLA, allowing users to click and initiate a new search in real time, retrieving the latest relevant citations. The

embedded searches are limited to the free databases PubMed and AGRICOLA; search strategies are provided for proprietary databases, i.e. BIOSIS, with instructions on how to copy and paste, thereby facilitating an effective search. These comprehensive search strategies illustrate that alternatives are just one part of a thorough search, which includes multiple databases and multiple search strategies.

2.7.2 Alternatives in education

The USDA requires principal investigators to consider alternatives to veterinary medicine teaching protocols containing procedures that may cause more than momentary or slight pain or distress to the animals. In response, the UCCAA developed search grids for protocols of alternative methods for veterinary medicine instruction. These grids make use of the same comprehensive searching approach advised for all protocols, emphasising the consideration of the 3Rs, and using multiple databases. Teaching protocols require searches in several of the traditional bibliographic databases, such as MEDLINE, CAB Abstracts, and AGRICOLA, but also in alternatives' databases such as NORINA and AVAR. The alternatives databases specifically catalogue and provide live links to products on alternatives, such as life-like models, videos and software.

3 Indexing systems for alternative methods

As reported in the literature, one important prerequisite for adequate information retrieval is an appropriate information indexing system (Allen, 1997; Bottrill, 1999; Firestein et al., 2000; Salton et al., 1986; Huggins, 1994; Bottrill et al., 2000; Nelson, 2002). Indexing is used to highlight database content or other information sources, e.g. websites, to facilitate a search. According to the British indexing standard (BS3700: 1998), an index is a systematic arrangement of terms (keywords) designed to enable users to locate information. In a thesaurus, these terms are grouped hierarchically and according to related groups of terms. In comparison,

keyword lists are organised in alphabetic order. Indexing assigns publications with representative terms to narrow search options. Indexing is either conducted by an indexer or an automatic indexing programme. The existing indexing systems are database-specific, e.g. indexing information on alternative methods is different in each database.

3.1 The NAL Agricultural Thesaurus (NALT): a tool for information organisation and retrieval

<http://agclass.nal.usda.gov/agt/agt.htm>

A thesaurus intends to arrange terms in a structured format to help find terms of possible interest. It provides a common language that can be used for compatibility across systems. The aim is to call up all related items by a retrieval system and to allow the user find the relevant information by limiting unnecessary search results.

The NAL Agricultural Thesaurus (NALT) was developed by the NAL (USA) to meet the needs of the Agricultural Research Service (ARS) of the USDA for modern agricultural terms. The first edition of the NALT was released in 2001. In 2003, the NAL implemented the thesaurus as a controlled vocabulary of NAL's bibliographic database AGRICOLA. NALT is used as a supplement to the CAB Abstracts thesaurus, which is the original AGRICOLA indexing system.

The Food Safety Research Information Office (FSIRO) and the Agricultural Network Information Center (AgNIC) use the NALT as the controlled vocabulary in their information systems. NALT is used to browse the ARS and AgNIC websites, and to index USDA research projects. Furthermore, it is used to set up metadata on the NAL websites.

In January 2004, the third edition of the NALT was published containing approximately 62,000 terms. The terms used for the NALT are chosen from reference works, databases, other thesauri, and Internet sites. The NALT will be updated yearly in January. Thesaurus staff reviews potential new terms. Selected terms are defined and placed in the thesaurus structure. About 5000 terms are scheduled for addition to the 2004



edition. About half of these terms are taxonomic terms. Suggested terms are selected for inclusion according to their frequency of use and importance in agriculture. Terms are verified using a variety of authorities. Until now, there has been a retroactive conversion of 3 million AGRICOLA records.

The structure of NALT is based on ANSI/ISO Z39.19 "Guidelines for the Construction, Format, and Management of Monolingual Thesauri" published by the National Information Standards Organisation (NISO, USA), which is equivalent to the international standard ISO 2788. The use of the international standard makes it compatible with other systems using ISO.

The NALT is structured poly-hierarchically, which means that terms may be used in several places; for example "forestry law" can be found under "forestry" and under "law". The thesaurus is organised into 17 subject categories that include hierarchical, equivalence and associative relationships among the terms. Hierarchical relation-

ships are indicated by "Broader Terms" and "Narrow Terms" designations. Equivalence relationships are defined by "Use" and "Use for" cross-references. Associative relationships are designated by "Related Terms". Each single term is assigned to one concept only. For example, "animal models" is only used for animal models of human diseases. In addition, scope notes and definitions have been included to clarify the meaning of the terms.

NALT includes terms that are used to index documents relating to alternatives to animal experiments. The subject category "Animal Science and Animal Products" in the thesaurus is subdivided into 10 terms, one of which is named "Animal Welfare". Animal Welfare is defined here as "The sum or integration of an animal's past and present state of well-being as it attempts to cope with its environment; and human value concerning the social or ethical aspects of providing that environment." "Animal Use Alternatives" is listed under the term "Animal Welfare" as one of the related

terms. At the next level the NALT breaks down the term "Animal Use Alternatives" into the terms "Animal Use Reduction", "Animal Use Refinement", and "Animal Use Replacement". These terms correspond with the definition of the 3Rs of Russell and Burch (1959).

Indexers at NAL index the alternatives literature in the NAL database AGRICOLA using this vocabulary. Materials indexed for the database include peer reviewed journal articles, conference proceedings, books, audiovisuals, and all AWIC-produced publications that address the broad spectrum of research relating to the 3Rs and other areas of animal welfare such as care of pet, zoo and farm animals.

As in taxonomy, a thesaurus is never "complete" (Milstead, 1998). Maintaining the usefulness of the NALT requires ongoing commitment to updating. New alternative terminology must be added, existing terms changed, and occasionally deleted. The NALT staff invites suggestions and changes to the thesaurus and / or suggestions for new terms using a

Tab. 2: Index terms for alternative methods used by MEDLINE, EMBASE, AGRIS, CAB Abstracts and AGRICOLA databases in 2002

Database	Subject	Thesaurus	Relevant Terms
MEDLINE National Library of Medicine (NLM), USA http://www.nlm.nih.gov	Biomedicine and Related Fields	Medical Subject Headings (MeSH)	Animal Testing Alternatives Animal Use Alternatives
EMBASE Elsevier Science, NL http://www.elsevier.nl	Biomedicine and Related Fields	EMTREE	Animal Testing Reduction Animal Testing Alternatives Animal Testing Refinement Animal Testing Replacement
AGRIS United Nations Food and Agriculture Organisation (FAO) http://www.fao.org/agris	Agricultural Sciences and Related Fields including Veterinary Sciences	AGROVOC	Animal Testing Alternatives
CAB Abstracts Commonwealth Agricultural Bureau International (CAB), UK http://www.cabi.org	Agricultural Sciences and Related Fields including Veterinary Sciences	CAB Thesaurus	Animal Testing Alternatives
AGRICOLA National Agricultural Library (NAL), USA http://www.nal.usda.gov	Agricultural Sciences and Related Fields including Veterinary Sciences	CAB Thesaurus; NALT	Animal Testing Alternatives Animal Use Alternatives Animal Use Reduction Animal Use Refinement Animal Use Replacement



form available at <http://agclass.nal.usda.gov/agt/contact1.htm>. Furthermore, the NALT staff will become more active in investigating the following issues:

- mergers of vocabularies that already exist,
- feasibility and usefulness of translation to other languages,
- needs of comprehensiveness,
- collaboration with international groups to expand the body of terms, and
- enhancement of the search engine to rank search results.

3.2 Indexing systems for alternative methods – a ZEBET investigation

3.2.1 ZEBET's investigation on indexing systems on the Internet

Currently, a wide range of information resources, e.g. databases and websites offer scientific information on alternative methods. Based on their experience in documentation, indexing and searching for alternative methods, the ZEBET staff is evaluating whether the information available in the database resources is sufficient to fulfil the demands of animal welfare legislation, and whether scientists can retrieve the required information.

In 2002, ZEBET began its investigations on indexing systems of alternative methods in established literature databases. The goal was to determine how

alternative methods are indexed and how search results for alternatives are influenced by different procedures of indexing information. ZEBET presented the first results of the study at the workshop in 2003.

3.2.2 Results of ZEBET's investigations

Meissner compared different database indexing systems for alternative methods in co-operation with ZEBET in 2002 (Meissner, 2002). The databases MEDLINE, EMBASE, AGRIS, CAB Abstracts and AGRICOLA use a variety of terms for alternative methods as illustrated in Table 2.

For example, the MeSH term “Animal Use Alternatives” is defined by the NLM (2003) as follows: “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 phylogenetically lower species, or refinement of methods to minimise pain or distress of animals used.”

Taking into account Meissner's evaluation, ZEBET developed a search approach according to the following criteria:

• Databases searched

In order to allow comparison of relevant database contents, the following databases were selected:
MEDLINE (ME83), established in 1983 (7.8 million documents)

EMBASE (EM83), established in 1983 (6.9 million documents)

AGRIS (AG86), established in 1986 (2.0 million documents)

CAB Abstracts (CV72), established in 1972 (4.3 million documents)

AGRICOLA (file “Books” and “Articles”), established in 1970 (3.7 million documents)

• Search terms used

ZEBET searched a total of 44 terms including eight general search terms for alternative methods in the selected databases identified by Meissner (2002), 15 search terms for specific alternative methods, e.g. acute toxic class method, and 21 search terms on other relevant topics, e.g. acute oral toxicity. These specific search terms were taken from the AnimAlt-ZEBET keyword list according to their relevance to alternative methods.

The study was conducted in 2002. Access to MEDLINE, EMBASE, AGRIS, and CAB Abstracts databases was obtained via DIMDI. AGRICOLA was accessed directly via <http://www.nal.usda.gov> and searched in free text search mode to find all available documents containing information on alternative methods in any accessible data field of the documents. A phrase search was used via DIMDI and “any keyword search” was used for AGRICOLA. In AGRICOLA the search terms needed to be combined by the operator “AND”.

Tab. 3: Numbers of publications retrieved on alternative methods in MEDLINE, EMBASE, AGRIS, CAB Abstracts, and AGRICOLA in October 2002

Search Terms	MEDLINE 7.8 Mio documents	Embase 6.9 Mio documents	Agris 2 Mio documents	CAB Abstracts 4.3 Mio documents	AGRICOLA 3.7 Mio documents
animal testing alternatives	1,023*	0	418*	213*	968*
animal testing reduction	0	27*	0	0	88
animal testing refinement	0	19*	0	0	45
animal testing replacement	0	21*	0	0	439
animal use alternatives	33*	0	1	1	345*
animal use reduction	0	0	0	1	213*
animal use replacement	0	0	0	0	112*
animal use refinement	0	0	0	0	253*
Total Hits	1,056	67	419	215	2,463

* Indexed Terms



The first search used only the eight index terms for alternative methods. In Table 3, search results from the five databases are summarised. The number of records retrieved indicates that MEDLINE, EMBASE, AGRIS, CAB Abstracts, and AGRICOLA index alternative methods at varying frequencies. 2263 references were found in AGRICOLA and 1056 in MEDLINE. In EMBASE, AGRIS, and CAB Abstracts less than 500 references each were found. It may be concluded that AGRICOLA allocates the terms more frequently compared to the other databases, regardless of the specific modus used in AGRICOLA.

In the next step, the search for alternative methods was combined with evaluated search terms for specific alternative methods and terms for relevant topics. The search for publications on “monoclonal antibodies” is presented as an example in Table 4. The *in vitro* production of monoclonal antibodies is important to replace the *in vivo* procedure employing the ascites tumour mouse model. During the past decade, *in vitro* techniques have been developed, which allow production of monoclonal antibodies in mouse hybridoma tumour cells without using mice at all. These include the culture of hybridoma cells in dialysis

tubing and hollow fibre bioreactors, e.g. the Technomouse™.

In Table 4 the combination of the search results for alternative methods to produce monoclonal antibodies shows a significant decrease in the number of hits recorded. The search for this topic retrieved only 11 records in MEDLINE and in AGRICOLA. In AGRIS and CAB Abstracts less than 10 references were found and EMBASE did not yield any references at all. The results illustrated in Table 4 represent a typical example of a search result. A comprehensive report of the results of ZEBET's investigation is currently being prepared.

3.2.3 Discussion of the results of ZEBET's investigation

When databases were compared, the preliminary search results indicated that AGRICOLA identified more publications on alternative methods than other databases. This result should be examined more closely and confirmed by a more extended search. A strong decrease in the number of publications retrieved was observed when search terms for alternative methods were combined with search terms for a given alternative method and more specific search terms.

Compared to the number of references quoted in the documents of AnimAlt-

ZEBET, the low number of hits scored in a search with only three search steps showed an even more dramatic failure of information retrieval. AnimAlt-ZEBET contained 115 documents with approximately 6000 bibliographic references in November 2003. The highest number of indexed publications retrieved from a search was from AGRICOLA with approximately 2500 records. Furthermore, a search in AnimAlt-ZEBET provided four documents relating to *in vitro* methods of producing monoclonal antibodies with 79 bibliographic references. The search for this topic in both MEDLINE and AGRICOLA provided only 11 records each.

The results of the study show that none of the existing databases completely covers all alternative methods and that this may lead to a loss of relevant information due to deficits in indexing, since not all relevant publications could be retrieved. At the same time, our AnimAlt-ZEBET database covers only a limited number of alternative methods.

Thus, ZEBET puts forward the following hypothesis to be discussed by information retrieval professionals:

Indexing systems are not (yet) used to their full potential since not all of the relevant information is indexed as “alternative methods”. As a consequence, not

Tab. 4: Numbers of publications retrieved on alternative methods and the subject of monoclonal antibodies in MEDLINE, EMBASE, AGRIS, CAB Abstracts, and AGRICOLA in 2002

Search Terms	MEDLINE 7.8 Mio documents	Embase 6.9 Mio documents	Agris 2 Mio documents	CAB Abstracts 4.3 Mio documents	AGRICOLA 3.7 Mio documents
animal testing alternatives	1,023	0	418	213	968
animal testing reduction	0	27	0	0	88
animal testing refinement	0	19	0	0	45
animal testing replacement	0	21	0	0	439
animal use alternatives	33	0	1	1	345
animal use reduction	0	0	0	1	213
animal use replacement	0	0	0	0	112
animal use refinement	0	0	0	0	253
Total Hits	1,056	67	419	215	2,463
Monoclonal antibod?*	109,535	125,467	5,532	17,332	5,188
Monoclonal antibod?*	11	0	3	6	11
AND Total Hits for alternative methods					

*The term “monoclonal antibodies” was truncated to include singular and plural forms of the word antibody.

all of the relevant literature on alternative methods is covered by the search terms “Animal Testing Alternatives” or “Animal Use Alternatives”.

This deficit may result from the current indexing rules. Nelson (2002) explains, that publications are indexed according to content but not according to their potential relevance to alternatives to animal experiments. If the text of an article does not specifically indicate that its content relates to an alternative method, i.e. the terms for alternative methods are not used in the text, it cannot be indexed under the terms covering alternatives to animal experiments.

3.2.4 ZEBET's suggestions for the way forward

Taking into account the results of the investigation on indexing systems on the Internet, ZEBET proposes the following topics for further discussion and investigation:

- **Development of “Good Searching Practices” for alternative methods**
“Good Searching Practices” for alternative methods should allow the use of the most specific search profile reflecting the type of research for which alternative methods are applied. Currently, searches using the keywords “animal testing alternative” and/or “animal use alternative” can only serve as supplements. Searching in a super-base mode (multi-database searching technique) should become the accepted standard.
- **Establishing specialised databases and websites**
Databases and websites on alternative methods, e.g. ECVAM-SIS, ALTBIB, AWIC, Altweb, UCCAA, and AnimAlt-ZEBET, have the advantage of providing selected information on specific subjects. These sources of specific information should be incorporated into regular searches for alternative methods.
- **Improving the Current Indexing Systems**
The indexing systems should include an evaluation whether the bibliographic references encompass alternative methods. In addition, limitations and advantages of automatically processed indexing systems should be investigated.

4 Conclusions and recommendations of the Berlin workshop

The workshop showed that a huge amount of information on alternative methods is available on the Internet. However, the existing sources of information differ in content, structure, quality of information and search tools. Established bibliographic databases, e.g. MEDLINE and AGRICOLA, offer comprehensive documentation on scientific publications. Specialised databases, e.g. ALTBIB, ECVAM-SIS and AnimAlt-ZEBET, provide pre-selected information and present accessible, relevant information on a single website.

It is in the highest interest of information providers to ensure that the relevant information is reliably accessible, especially considering that according to U.S. Animal Welfare Regulation and Public Health Service Policy (United States Department of Agriculture, 1997 and 2000) and European Directive 86/609/EEC, scientists should conduct a complete search for literature and other relevant information on alternatives to avoid unnecessary animal experiments, unnecessary pain or distress to the animals and unnecessary duplication of animal experiments.

The participants of the workshop developed the following recommendations and work proposals to improve the information retrieval on alternative methods on the Internet.

4.1 Development of web-based search strategies

Web-based search tools should be developed to enable scientists to conduct and document a complete search for literature on alternatives to animal experiments.

Search tools should include search algorithms with suitable search terms. Search profiles including search steps, the use of Boolean operators and limitations should be explained in a user-friendly manner. In addition, searches based on multi-database formats, as well as recommendations for databases supporting appropriate search strategies should be discussed.

The application of web-based search strategies will depend on their acceptance by scientists as well as authorities, for example the IACUCs in the USA and the Animal Protection Officers in Europe.

4.2 Development of the AWIC “Literature Search for Alternatives Worksheet”

The workshop members discussed how to improve the acceptance of the AWIC worksheet by the scientific community. AWIC invited recommendations for revision of the forms, emphasising consideration of user-friendly accessibility and comprehensibility. Translating the worksheet into common European languages, e.g. German, was also recommended.

4.3 Improvement of indexing of alternative methods by the authors and/or editors of scientific journals

By using appropriate keywords when indexing publications related to alternative methods, authors and/or editors of scientific journals can play a crucial role in making alternatives available to the scientific community. Scientific journals such as “Alternatives to Laboratory Animals” (ATLA, UK) and “Alternativen zu Tierexperimenten” (ALTEX, Germany) are good examples for appropriate indexing of alternative methods.

The workshop members recommended that the application of index terms such as “Animal Testing Alternatives”, “Animal Use Alternatives”, “Animal Use Reduction”, “Animal Use Refinement”, and/or “Animal Use Replacement” by authors and editors should follow the definition used by the NLM’s MeSH and the NAL’s AGRICOLA Thesaurus. Practical instruction should be prepared and discussed by scientific authorities including animal welfare information services in co-operation with the editors of scientific journals.

4.4 Improving current indexing systems

Every database has its own indexing system, including stringent procedures to add new terms, to change or to delete existing terms and/or hierarchies. The



expertise of the information centres for alternative methods should be taken into account when updating or extending a thesaurus.

For example, as mentioned above, the NALT staff (AGRICOLA) invites suggestions and changes to the thesaurus using a form that is available at <http://agclass.nal.usda.gov/agt/contact1.htm>.

4.5 Search training programmes

There are a number of established training programmes on searching for alternative methods in databases. For example, AWIC (NAL, USA) regularly offers workshops entitled, "Meeting the Information Requirements of the Animal Welfare Act". This is a free one-and-a-half-day workshop intended for biomedical scientists, members of IACUCs, and information providers. The use of existing databases and information networks is covered in the AWIC workshops. (<http://www.nal.usda.gov/awic/awicworkshops/awicworkshops.htm>).

The Berlin Workshop members recommend increasing and extending training opportunities, following the AWIC model. Scientists, IACUC members (USA), Animal Protection Officers and representatives of the ethics committees and the local authorities of the states (EU), who are trained in developing appropriate search strategies, will be able to improve their search results, identify weak points, inefficiencies, and/or discrepancies in the submitted protocols.

The workshop also concluded that when new tools for searching and manipulating search results are developed, emphasis should be placed on making them as convenient as possible for scientists and review committees. Given the ethical and legal importance of compliance, limitations to utilising search tools should be minimised.

4.6 Development of research programmes

The development of search strategy programmes that are able to convert a simple search question into a suitable complex search protocol should be discussed in an interdisciplinary dialogue between biomedical and information scientists. It is a challenge to develop an intelligent "search engine" that will translate in-

quiries of biomedical scientists into a professional search on alternative methods. Due to the rapid pace of advances in database search technology, the group was optimistic that web-based aids for conducting searches for alternatives will become more feasible.

For many years the information centres for alternative methods, both in the US and Europe, have developed and refined their search strategies. They have gained experience in all aspects of information searching. The knowledge of these experts on information searching should, therefore, be used when new research strategies on alternatives are established.

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