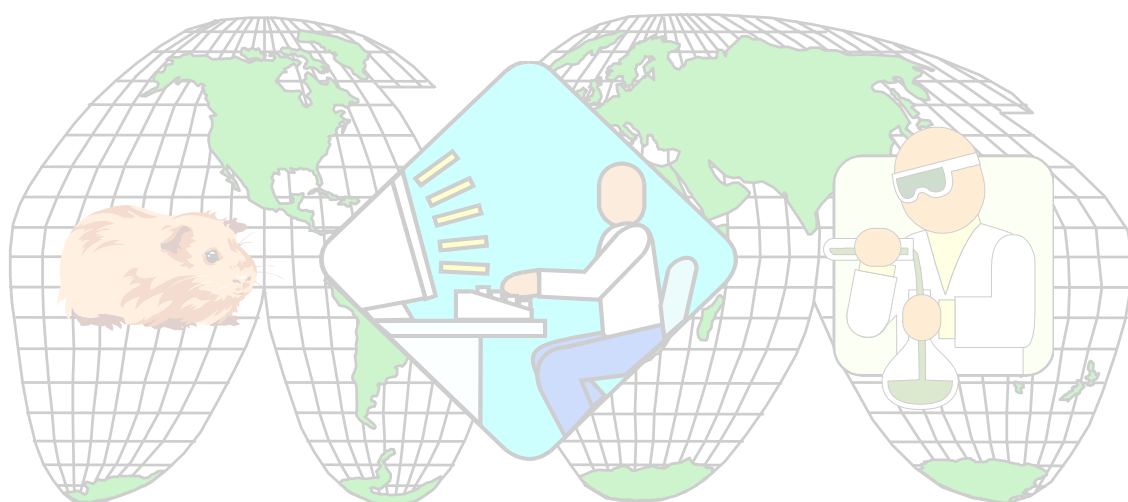


Information Managers in the Pharmaceutical Industry

I3R Working Party

Searching for 3Rs Information - Published Literature Sources



2nd Edition
July 2002

Searching for 3Rs information - published literature sources

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Executive Summary

There is a legal and ethical obligation to reduce the numbers of animals in research and to enhance the welfare of those that are used. This has led to an increased need for access to information on this topic.

To help meet these obligations, members of the UK Pharmaceutical Industry set up a working party of information experts (I3R) with the aim "to encourage the development of best practice in the provision and retrieval of information on alternatives to animals in pharmaceutical R&D with special reference to Refinement, Reduction and Replacement (3Rs)."

The I3R group produced the first edition of this document in January 2001 to assist researchers and information professionals in the pharmaceutical industry to retrieve relevant information on animal alternatives and the 3Rs. The document has been updated (July 2002) following discussions with biomedical database producers to improve the source material (journal coverage) and search capabilities for 3Rs information in their databases.

Included in the document are sections covering:

- core 3Rs journal coverage across 12 key bibliographic databases
- details of scope, strengths & weaknesses, and useful search terms for each database
- a list of keywords useful for 3Rs and animal alternatives searching
- an example generic search strategy
- selected other information resources

Summary of changes since first edition

- Increased journal coverage in Biosis, Chemical Abstracts, Embase and Medline (details in Table 1)
- Elsevier have expanded Emtree in response to recommendations made by the IMPI I3R Working Party (see database details)
- Medline have introduced a new MeSH term (see database details)
- Database sheets have been updated to reflect any changes

Recommendations

To help overcome the issues faced by researchers and information professionals when searching for information on the 3Rs and alternatives, the following points should be considered.

- As a minimum, the following 4 databases should always be searched: Medline, Embase, Biosis, and Science Citation Index.
- The more databases that are searched, the more useful information you will find.

- Consider a search of the patent literature.
- There are specific journals on the subject of animal alternatives but be aware that 3Rs related literature can be published in almost any scientific journal.
- Be prepared to scan many titles of references retrieved by a search strategy, as relevant references will be diluted by those that are irrelevant however focussed the strategy. Also, proving a negative is harder than finding a positive.
- Use all possible synonyms and phrases (refer to keyword list) and build a search strategy (refer to generic strategy) before going online.
- Prepare for a search to evolve in a continuing dialogue between the researcher and the information professional.
- An information professional should be consulted for all Home Office project licence applications.
- For a literature search to support a Home Office project licence use a 2 stage process: try the general terms for alternatives in conjunction with the disease or subject area, then concentrate on specific searches on models, procedures etc.

Database producers may introduce new indexing terms or make other changes. Always refer to the database producer for the latest information.

Introduction

IMPI and I3R

Information Managers in the Pharmaceutical Industry (IMPI) is a forum for UK based Information Managers in the pharmaceutical industry to share, agree and resolve common issues relating to information and knowledge management.

IMPI serves as a pressure group to represent industry-wide information needs to suppliers of information products and services, thus leveraging the power of the UK pharmaceutical industry to influence appropriate product development.

IMPI is affiliated to the Pharma Documentation Ring (PDR), a Europe-wide group with similar objectives. IMPI is thus able to represent a co-ordinated UK position to the PDR on information and knowledge management issues.

The working party on 3Rs (I3R) was set up in December 1999 with the initial aim to explore scope for collaboration in improving retrieval and providing information to support the refinement, reduction or replacement of animals used in drug research and development. The objective of the group was agreed:

"To encourage the development of best practice in the provision and retrieval of information on alternatives to animals in pharmaceutical R&D with special reference to refinement, reduction and replacement (3Rs)."

Specific activities include:

- Knowledge sharing on published information sources (databases, journals etc)
- Evaluation and categorisation of sources
- Influencing database producers, journal publishers and authors to highlight 3Rs content and issues
- Liaison with regulatory authorities and other interested parties.

The role of the information scientist

Information scientists are experts at retrieving scientific information, including information relating to 3Rs issues, and they are able to provide a link between the researcher and the plethora of information sources that are available.

Researchers can search some published information sources for themselves, but for comprehensive coverage they should also consult an information professional, who specialises in locating and searching a wide variety of information sources, including those that are not generally available to the end-user. Information scientists are familiar with a broad spectrum of databases and know the best way to search them using appropriate database-specific controlled indexing. By combining the researcher's detailed

subject knowledge with the information professional's searching skills and scientific background, a creative and productive partnership can evolve.

3Rs and alternatives to animals

There is a legal and ethical obligation to reduce the numbers of animals in research and to enhance the welfare of those that are used.

In the UK the use of animals for research purposes is governed by the Animals (Scientific Procedures) Act 1986¹ and licences for such work are granted by the Home Office. The Home Office requires that efforts are made to identify alternative methods to the use of animals, and ways to refine, reduce or replace the use of animals. In addition, when applying for a project licence it must be demonstrated that searches for alternative methods to the use of animals have been carried out, and in some cases, Home Office Inspectors have requested to see the references retrieved by such a search, together with the search strategy used.

In 1954 a project initiated by the Universities Federation for Animal Welfare (UFAW), led to the concept of the 3Rs of reduction, refinement and replacement which was published in *The Principles of Humane Experimental Technique* by Russell and Burch² in 1959. In 1978 David Smyth³ of the Research Defence Society (RDS) used the word *alternatives* to encompass all of the 3Rs.

The Three Rs Declaration of Bologna as adopted by the 3rd World Congress on Alternatives and Animal Use in the Life Sciences (31 August 1999)⁴ defines the 3Rs as follows:

*"Reduction alternatives - methods for obtaining comparable levels of information from the use of fewer animals in scientific procedures, or for obtaining more information from the same number of animals.
Refinement alternatives - methods which alleviate or minimise potential pain, suffering and distress, and which enhance animal well-being.
Replacement alternatives - methods which permit a given purpose to be achieved without conducting experiments or other scientific procedures on animals."*

3Rs information

Information resources on the 3Rs and alternatives encompass many types - primary literature sources, bibliographic databases, specialist collections, organisation websites and factsheets, books and monographs, discussion groups, software and audiovisual material.

Many scientists and researchers use databases such as Medline but relevant information is often difficult to retrieve due to their lack of focus on the 3Rs and alternatives.

In fact searching the literature can provide much information on alternative methods which lead to reduction, refinement or replacement of animal procedures in research. Papers of relevance can be published in almost any type of journal not necessarily one specifically concentrating on alternatives or methods and therefore the major biomedical literature databases, Medline, Biosis, Embase, and Science Citation Index, are the key databases for alternatives/3Rs literature. Valuable information can also be obtained from other databases and patent literature. So, when trying to identify a way to reduce, refine or replace the need for animals in an experiment a search of the literature is vital. In addition there is a need to look at experimental design and various other ways to replace animals; the UFAW/FRAME guide *Selection and Use of Replacement Methods in Animal Experimentation* gives practical advice on where to start ⁵.

The I3R group have concentrated on how to search bibliographic databases effectively, although other information resources are suggested in a separate section (page 29). Problems that scientists and information specialists face when searching databases include the variability of journal coverage and limitations of indexing terms to aid retrieval. I3R attempt to address some of these issues and give some practical guidance to anyone searching the published literature for 3Rs information.

Published literature sources

Journals and database coverage

A representative list of journals with a high 3Rs content was compiled, based on the experience of the I3R members and on the results of a simple search strategy to rank relevant journal titles according to their 3Rs coverage.

Eleven (mainly biomedical) databases were then searched to determine how many of these journals were abstracted and how many articles there were for each journal during the time period 1995 - June 2000. The results are shown in the table on page 7. The major biomedical databases mentioned above were searched first, as is reflected in the table.

There was considerable variation of journal coverage across the different databases. Broadest coverage, for that time period, was provided by CAB International (12 titles), Science Citation Index (11 titles) and Biosis/Current Contents/Toxline/Agricola (10 titles each), although no single database included all journal titles. Notably the "popular" biomedical databases Medline (5 titles) and Embase (6 titles) did not do so well. It is recognised that journal coverage is constantly evolving and that titles may be added or dropped; for example, Biosis, Embase, Medline and Chemical Abstracts have all included extra 3Rs journals since June 2000.

The high number of dedicated 3Rs journals in CAB International reflects its good coverage of animal welfare/husbandry, whereas, the relatively low number in Medline and Embase for the time period 1995 to June 2000 does not reflect the strength of these sources for a wide range of 3Rs/alternatives literature, particularly *in vitro* methodology needed to identify alternative methods to animals. This apparent discrepancy arises because the majority of 3Rs/alternatives papers are published in a wide range of journals not focussed on 3Rs issues.

These results emphasise the importance of including a range of databases in any search strategy to maximise relevant retrieval.

Comparison of Journal Coverage by Database January 1995 to June 2000 –Annotated For Journals Added Since June 2000 (√)

Journal	Medline	Embase	BIOSIS	Current Contents	Science Citation Index	Toxline	Derwent Drug File	Chemical Abs	CAB Intl	Pascal	Agricola
Animal Welfare			173	112	112	2		√	172	14	89
ATLA Alternatives to Laboratory Animals	√	97	√	582	600	14		√	69	256	167
AWIC Bulletin								√	32		47
Contemporary Topics in Laboratory Animal Science	√		60	31	276	3		√	116		
Devs in Biological Standardization (now Devs in Biologicals)	721	√	633		302	150		585	63	598	271
Experimental Animals (Tokyo)	296		309	142	309	66		122	136	112	15
ILAR Journal (Inst of Laboratory Animal Research)	√							√			58
J Applied Animal Welfare Science	19		224					√			34
J Experimental Animal Science	659	93	86	108	113	6	1	48	59		
Laboratory Animal Science (Now Comparative Medicine)	332	648 (35)	644	602 (34)	624 (34)	130	10	149(7)	417(8)		469
Laboratory Animals (London)	√	299	292	322	322	59		94	204	308	451
Scandinavian J of Laboratory Animal Science				..				√	122		
Sciences et techniques de l'animal de laboratoire	√		√	73	83			√			
Toxicology in vitro	√	525	645	520	541	502		598	18	499	
Toxicology Methods		53	53	125	131	33		215	1		1

1. Not all journals are included for the full time period (1995 to June 2000) eg. Embase only started covering ATLA in 1999.
 2. Depending on the database, some journals are considered to be priority and are covered in more depth than other journals. Some are indexed cover-to-cover and some are selectively screened. For example, over the time period January 1995 – 2000, Toxline has only 59 records from Laboratory Animals (London) whereas Medline has 332. Toxline has selected only those papers with a high toxicology content.
 3. A number of the journals have changed their titles (sometimes more than once), and not all versions are included here. In addition, a few of the journals have very similar titles, but are independent publications, and this was not always easy to establish.
- √ Journal has been added to database since January 2001

Patents as Sources of 3R Information

In addition to journal articles and conference reports, account must be taken of the valuable and important information on the 3Rs contained in the patent literature.

It is strongly recommended that a source of patent literature be included in the course of a search for 3Rs information for the following reasons:

- A significant proportion of current pharmaceutical related patents are research tools e.g. assays, reagents or methodologies.
- 70% of the information contained in patents is not published elsewhere, and even when it is, the patent will usually have been the earliest mention.
- Significant and practical inventions are patented - the better or more commercially important an idea, the more likely that it is to have been patented.
- Patent information may save money in duplicated research costs e.g. licensing a patented technology.
- Information may already be in the patent literature that facilitates a solution to a difficult problem.

Basic patent literature can be found in Chemical Abstracts (includes more than 2.6 million chemistry related patent families) and Derwent World Drug Alerts (includes more than 80,000 pharmaceutical patents). Details of how to search these databases are included in the database details section of this document.

NB Infringement of patents may lead to expensive litigation. A search of patent literature can identify if and where there is a conflict and strategies can be adjusted or agreements made with patent holders. Therefore, for business critical research information, an extensive search of specialist patent databases by patent experts should be undertaken.

Database details

The following pages contain details of the key databases listed below:

- Agricola
- BIOSIS
- CAB International
- Chemical Abstracts
- Derwent Drug File
- Derwent World Drug Alerts
- Embase
- Medline
- Pascal
- Science Citation Index
- Toxcenter - ToxFile (formerly Toxline)

NB The descriptors or codes indicated are expressed in DataStar language with the exception of Chemical Abstracts which are in STN language.

Agricola

PRODUCER National Agricultural Library (NAL) of the U.S. Department of Agriculture (USDA),
 Beltsville, MD 20705, USA.
 e-mail: ag98help@nal.usda.gov
 Tel +301 504 5755
 Website <http://www.nalusda.gov/> (NAL-USDA). <http://www.nalusda.gov/ag98/> (Agricola)

SCOPE OF DATABASE

Coverage: 1970 to present on Dialog and STN. Also available free at url given above.
 Subjects covered are all aspects of agriculture, including animal and plant sciences, cytology, entomology, feed science, food and nutrition, microbiology, physiology, veterinary medicine, and zoology. The database contains over 3,554,000 records, from 2,000 journals. Only 10% of records have an abstract. The veterinary science and animal husbandry content makes Agricola a good source of animal refinement/welfare references. Updated monthly. Agricola covers 10 of our listed 15 core journals.

STRENGTHS & WEAKNESSES

Since 1985, the *CAB Thesaurus* has been used to select controlled vocabulary terms. Indexing includes 1) descriptors (DE field), 2) Section Headings (SH field), and 3) Identifiers (ID field).
 The descriptor "animal-testing-alternatives" is used as an indexing term in 839 references.

USEFUL TERMS FOR SEARCHING

TOPIC	DESCRIPTOR/CODE
General Topics : Ethics animal welfare methods and procedures	Bioethics Animal-welfare.DE. Techniques.DE.
Replacement Topics : in-vitro cell culture human tissue model mathematical physicochemical computer lower organisms bacteria fungi insecta	In-vitro.DE. Cell-culture.DE., cell-line.DE., tissue-culture.DE., Human.DE. Mathematical-models.DE. Models-and-molecular-conformation.DE. Simulation-models.DE Computer-simulation.DE. Bacteria.DE. Fungi.DE. Insects.DE.
Reduction Topics : Experimental design statistical concepts quality control	Animal-reduction.ID. Experimental-design.DE. Statistical-analysis.DE. Mathematics-and-statistics.SH. Quality control.DE.
Refinement Topics : animal welfare animal husbandry animal behaviour pain stress	Animal-use-refinement.ID. Animal-welfare, Animal health Animal-husbandry.DE., Animal-Production.SH. = L100.SH., Animal-Reproduction.SH. = L210.SH. Animal-behavior.DE. Pain.DE. Stress.DE.

BIOSIS

PRODUCER 2 Commerce Square,
2001 Market Street, Suite 700,
Philadelphia, PA 19103-7095, USA,
Tel +1 215 587 4800 (worldwide) 800 523 4806 (USA and Canada),
Fax: +1 215 587 2016, e-mail info@mail.biosis.org,
European Help-Desk:= Tel: +44 (0) 1904 642816, Fax: +44 (0) 1904 612793
European office email: helpdesk@york.biosis.org
Website <http://www.biosis.org>

SCOPE OF DATABASE

Coverage 1969/70 to present on DataStar (1970), on Dialog (1969) and STN (1969). Subject covered is all life science subjects, including Agriculture, Bacteriology, Behavioral Sciences, Biochemistry, Cell Biology, Experimental Medicine, Genetics, Microbiology, Pathology, Pharmacology, Physiology, Toxicology, Veterinary Science, Virology, Zoology. The database contains over 12,257,000 records, from 6,500 journals and includes meetings abstracts.. Updated weekly. BIOSIS has 9 of the 15 core journals. From 2002, Biosis Previews covers 12 of our 15 listed core journals.

STRENGTHS & WEAKNESSES

Records have a mixture of controlled and uncontrolled indexing with 1) Concept codes (CC field), which are controlled (NB the words describing these concept codes in the records are not searchable), 2) Supertaxa (ST field), which are also controlled, and 3) Descriptors (DE field), which are uncontrolled except for broad headings added to records after 1993. Descriptors can be searched as hyphenated terms, eg. In-vitro.de. or free-text at the same time as title and abstract terms, eg. Mathematical adj model\$1.ti,de,ab. There is no indexing for "alternatives to animals". This database is particularly strong in methods and techniques papers.

USEFUL TERMS FOR SEARCHING

TOPIC	DESCRIPTOR/CODE
General Topics : Methods and procedures	01004.CC. or Methods.DE. or method code for organ of interest, e.g. 16001.CC. for respiratory methods
Replacement Topics: in-vitro cell culture model mathematical physicochemical computer lower organisms bacteria fungii insecta	32600.CC. 32500.CC. 04500.CC. = Mathematical Biology and Statistical Methods 00530.CC. = Information Retrieval and Computer Applications. Microorganisms# Bacteria# Fungi# Insects#
Reduction Topics : Experimental design Statistical concepts Quality control	04500.CC. = Mathematical Biology and Statistical Methods
Refinement Topics : Animal welfare Animal husbandry Animal behaviour	28002.CC. Laboratory Animal Care 2650#.CC. 07003.CC.
Useful Major Concept terms	Method and techniques Models and simulations Animal Care

CAB International

PRODUCER CAB International
 Wallingford,
 Oxfordshire, OX10 8DE, UK.
 Tel +44 1491 832111 Fax +44 1491 826090
 e-mail: online@cabi.org (UK Help Desk)
 Website <http://www.cabi.org/>

SCOPE OF DATABASE

Coverage: 1973 to present on DataStar (CABI), Dialog, and STN. The VETS database on DataStar is 1984-present containing animal references from CABI. Subject coverage is agriculture, including, veterinary medicine, breeding & genetics, animal production, human & animal nutrition, biotechnology, human and animal parasitology and mycology. It contains 3,480,000 references, from 11,500 journals plus books and other sources. Updated monthly. CAB International covers 12 of our listed 15 core journals.

STRENGTHS & WEAKNESSES

Indexing is a mixture of controlled and uncontrolled terms and includes 1) Descriptors (DE field), which are uncontrolled 2) CABICODES (CC field) which are controlled and 3) Up-posted descriptors (UT field), which are controlled hierarchical terms.

The uncontrolled descriptor "animal-testing-alternatives" is rarely applied - 21 in VETS, 101 in CABI. The veterinary science and animal husbandry content of this database makes it a good source of animal refinement/welfare references.

USEFUL TERMS FOR SEARCHING

TOPIC	DESCRIPTOR/CODE
General Topics : Ethics Animal welfare Methods and procedures	Ethics.DE. AnimalWelfare.CC. = LL810.CC. Techniques & Methodology.CC. ZZ900.CC.
Replacement Topics: in-vitro cell culture human tissue model mathematical physicochemical computer lower organisms bacteria fungi insecta	In-vitro.DE. Embryo-culture.DE., Cell-culture.DE., In Vitro Culture of Animal Tissue.CC. = LL700.CC., Culture-techniques.DE. in-vitro-culture.DE., Homo.UT., Hominidae.UT. Mathematical-models.DE. Computer-simulation.DE., simulation- models.DE. Prokaryotes.UT. Bacteria.UT. Fungi.UT. Insects.DE.
Reduction Topics : Statistical concepts Quality control	Mathematics & Statistics.CC. = ZZ100.CC., Statistical-analysis.DE., Quality-control.DE.
Refinement Topics : Animal welfare Animal husbandry Animal behaviour Pain Stress	Animal welfare.CC. = LL810.CC. Animal-health.DE. Husbandry.CC. = (LL100,LL110, LL120, LL130, LL140, LL150).CC. Animal behaviour.CC. = LL300.CC. Pain.DE. Stress.DE.

Chemical Abstracts

PRODUCER Chemical Abstracts Service
 2540 Olentangy River Road
 PO Box 3012
 Columbus
 Ohio OH 43210-0012
 USA
 e-mail: help@cas.org
 Tel +1 614 447 3600
 Fax +1 614 447 3798
 Website <http://www.cas.org>

SCOPE OF DATABASE

CA is a bibliographic database covering international literature in chemistry and related fields. Life sciences constitute one-third of the database. For best results, the file should be searched on STN. Coverage: 1967 to date on Dialog and DataStar (bibliographic details and indexing only), 1907 to date on STN (bibliographic details and abstracts, indexing additionally available from 1967). It contains >19 million references from over 8,000 journals, in addition to patents and Web preprints. Cited references are included (STN only) since 1999. From 2002, Chemical Abstracts covers all 15 of our listed core journals.

STRENGTHS & WEAKNESSES

CA is very current, with daily updating and patent records added within 2 days of receipt. Indexing main headings are CAS Registry Numbers for chemical substances and Controlled Terms selected from the CA Headings List. These are modified by free text sub-headings. There are additional free text Supplementary Terms. On STN, chemical substances are further described by Roles and indexing terms may be looked up in the CAS Lexicon using the syntax: E 'term'+ALL/CT

USEFUL TERMS FOR SEARCHING

TOPIC		DESCRIPTOR/CODE
		Use CAS Lexicon on STN to find terms eg. E Cell culture+ALL/CT
General Topics :	Methods and techniques	Not specifically indexed. Search Free-text. Use Toxicology Section Codes (Sect4). Use BIOL Roles linked to CAS Registry Number(s)
Replacement Topics :	Animal Alternatives In-Vitro Models Computer Lower Organisms Bacteria Fungi Insects	Use (Animal or Toxicity)(L)alternatives/IT Use Free-Text Simulation and Modeling, physicochemical/CT Simulation and Modeling, Biological/CT Structure-Activity Relationship(L)toxic/IT Bacteria/CT, or more specific Indexing Term taken from 'Bergeys Manual' Fungi/CT, or more specific Indexing Term Insect (insecta) /CT, or more specific Indexing Term
Reduction Topics :		Statistical analysis/CT; Quality control/CT; Experimental design/CT
Refinement Topics :		Behavior/CT; Stress/CT

Derwent Drug File

PRODUCER Derwent Information
14 Great Queen Street
London
WC2B 5DF
United Kingdom
Tel: +44 (0)20 7344 2999
Fax: +44 (0)20 7344 2900
Website [http:// www.derwent.co.uk/prodserv/pharm/drug_file.html](http://www.derwent.co.uk/prodserv/pharm/drug_file.html)

SCOPE OF DATABASE

Coverage: 1983 to date on Dialog, Datastar and STN
The Derwent Drug File(DDF) covers all aspects of drug literature including chemical structures and synthesis, analysis, pharmacology, biochemistry, pharmaceuticals, toxicology, adverse effects. The database has more than 800,000 records from 1,200 journals. Approximately one third of records are conference abstracts. All records have an English language abstract.

The DDF covers only two of our listed core journals and only 11 records from these two journals are in the database since only articles with a strong drug/pharmacology aspect are selected for inclusion.

STRENGTHS & WEAKNESSES

The database uses extremely detailed, controlled-vocabulary indexing allowing very focussed retrieval of precise drug-related topics. There are no specific indexing terms for alternatives to animals. Overall the DDF is unlikely to contain information relevant to the 3Rs which cannot be found in the major biomedical databases.

USEFUL TERMS FOR SEARCHING

TOPIC	CODE
General Topics : methods and procedures	Method-ft Screening-method-ft
Replacement Topics : in vitro cell culture model lower organisms bacteria fungii insects	In-vitro-ft Tissue-culture-ft (higher term) Model-ft Bact-ft (higher term) Fungus-ft (higher term) Insect-ft
Reduction Topics : Statistical concepts quality control	Biometrics-ft (higher term) Quality-control-ft
Refinement Topics : animal behaviour pain stress	Animal-behavior-ft (higher term) Pain-ft Painful-ft Stress-ft Distress-ft

Derwent World Drug Alerts

PRODUCER Derwent Information
14 Great Queen Street
London, WC2B 5DF
United Kingdom
e-mail: custserv@derwent.co.uk
Tel: +44 171 344 2999
Fax: +44 171 344 2900
Website <http://www.derwent.co.uk>

SCOPE OF DATABASE

Database available on internet via Derwent Discovery, print, diskette or loaded on company intranet.

Coverage: 1994 to date and covers articles from 1,200 scientific and medical journals, conference reports and over 80,000 patents from seven major patent-issuing authorities (WO, EU, JP, US, GB, DE, FR). Information is focussed on all new chemical entities with potential therapeutic utility, diagnostic agents and methods, drug synthesis and pharmaceuticals. Updates weekly, articles included 1-3 weeks after publication.

WDA covers only 1 of our 15 listed core journals.

STRENGTHS & WEAKNESSES

Value added by expert classification, abstraction and indexing. Records classified according to drug activity, mechanism of action, compound name and document type. Records are also categorised into 11 subject-based areas, of particular interest are diagnostic agents, diagnostic methods and biotechnology.

Indexing terms for "screening", "diagnostic methods" and "diagnostic agents" available in combination with a specific "drug activity" or "mechanism of action" to aid in restricting the search to the required subject area. However, no adequate differentiation between methods involving animals and not involving animals. It may be possible to restrict results using the "Diagnosis-in-vivo" keyword.

USEFUL TERMS FOR SEARCHING

TOPIC	CODE
General Topics : Diagnostic Agents Diagnostic methods Biotechnology Drug activity = screening Drug activity = diagnosis-in-vivo Mechanism of action = Analysis	Subject area DS Subject area DM Subject area BT
Replacement Topics :	use free text
Reduction Topics :	use free text
Refinement Topics :	use free text

Embase

PRODUCER Elsevier Science
 Secondary Publishing Division
 Molenwerf 1
 1014 AG Amsterdam
 The Netherlands
 E-mail: embase-europe@elsevier.nl
 Tel: +31-20-485 3507
 Fax: +31-20-485 3507
 Website <http://www.elsevier.nl/homepage/sah/spd/embase/menu.htm>

SCOPE OF DATABASE

Coverage: 1974 to date on Dialog, Datastar and STN
 Subject coverage is biological science relevant to human medicine, biochemistry, biotechnology, toxicology, public health, psychiatry with special emphasis on drugs and pharmacology. Database contains over 9 million records from over 4000 journals. 80% of recent records contain full author abstracts.
 EMBASE covers 7 of our listed 15 core journals.

STRENGTHS & WEAKNESSES

Embase is very current with records added within 2 weeks of receipt of journal. Highly organised controlled indexing via the EMTREE Thesaurus can help with finding 3Rs information. Helpful sections of EMTREE include: J2 Types of Study; E5 Methods and Procedures; E5.275 Experimental Design; H3.830 Statistical Concepts; F2.90 Animal Behaviour; Q1.880 Toxicology; E1.880 Toxicity Testing. From 2002 new terms have been added narrower to the “animal-welfare” term – “experimental-animal-welfare”, “animal-testing-alternative”, “animal-testing-replacement”, “animal-testing-reduction” and “animal-testing-refinement”. New terms have also been added to the methodology and comparative study parts of the tree to aid more specific retrieval.

USEFUL TERMS FOR SEARCHING

TOPIC	DESCRIPTOR/CODE
General Topics: Ethics animal alternative methods	ethics# animal-testing-alternative# methodology#
Replacement Topics: animal testing replacement in-vitro cell culture human tissue model mathematical physicochemical computer lower organisms bacteria fungi insects comparative study	animal-testing-replacement in-vitro-study# model# bacterium# fungus# insect# comparative-study#
Reduction Topics: animal testing reduction experimental design statistics	animal-testing-reduction experimental-design (under methodology# statistical-concepts#
Refinement Topics: animal testing refinement/animal welfare animal behaviour pain stress	animal-testing-refinement or experimental-animal-welfare# animal-behavior pain# nociception# stress#

Medline

PRODUCER United States National Library of Medicine
 8600 Rockville Pike
 Bethesda, MD 20894
 USA
 e-mail: custserv@nlm.nih.gov
 Tel: +1 301-594-5983
 Fax: +1 301-496-0822
 Website <http://www.nlm.nih.gov/>

SCOPE OF DATABASE

Coverage: 1966 to date on Dialog, Datastar and STN; also available free as PubMed at www.ncbi.nlm.nih.gov/PubMed/

Covers all aspects of biomedicine including clinical medicine, anatomy, physiology, pharmacology, toxicology, genetics, psychiatry and psychology, environmental and public health, nursing, dentistry. Medline contains over 11 million records from 4300 journals. Abstracts are included for approximately 60% of records since 1975. Updated weekly. Medline covers 11 of our listed 15 core journals.

STRENGTHS & WEAKNESSES

There are terms in the Medline MeSH thesaurus which are useful for searching for 3Rs information but there is a lack of consistency in their assignment to individual records. "Animal-testing-alternatives" is available but it is usually only applied to papers describing ethical aspects of animal use. A new term introduced in 2001 "Animal-use-alternatives" is the broader term to "Animal-testing-alternatives". Helpful sections of MeSH include E5 Procedures and Techniques, E5-318-740 statistics, F1-145-113 Animal Behaviour, Toxicity Tests E5-940. Subheadings may be used to identify key aspects of articles: methods /MT, statistics /ST.

USEFUL TERMS FOR SEARCHING

TOPIC	DESCRIPTOR/CODE
General Topics: Ethics Animal alternatives Procedures	ethics# (includes bioethics) animal-use-alternatives# and the narrower animal-testing-alternatives investigative-techniques#
Replacement Topics: in vitro tissue culture models lower organisms bacteria fungi insects comparative study	Check tag tissue-culture# cell-line models-theoretical# bacteria# fungi# insects# Check tag
Reduction Topics: research design statistical concepts	research-design# statistics#
Refinement Topics: animal welfare animal husbandry animal behaviour pain	animal-welfare# (part of ethics tree) animal-husbandry behavior-animal# pain#

Pascal

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SCOPE OF DATABASE

Coverage: 1973 to present on Dialog (144), 1984 to present on Datastar (PASC) and STN. The subjects covered include pure and applied biology, homeopathy, medicine, botany, psychology, pharmacology, toxicology, biotechnology, agriculture, physics, chemistry, information science, telecommunications, construction industry, mechanical engineering, metallurgy, earth sciences, oceanography and astronomy. Fields NOT covered by Pascal include veterinary pathology (except infectious aspects) and animal husbandry (since 1979). The database contains over 13,000,000 records from over 8500 journals published worldwide, of which 4500 are abstracted completely. Pascal also covers conference proceedings, technical reports, books, patents (until 1980, and in biotechnology since 1983). Pascal covers 6 of our listed 15 core journals.

STRENGTHS & WEAKNESSES

Controlled terms from a vocabulary of over 80,000 terms are provided in English, French, and in some cases, Spanish. There are no special indexing terms for the concept of alternatives to animals. There are terms which are useful for retrieval of 3Rs information but there is a lack of consistency in their assignment to individual records. The terms which occur most commonly in hit records from a search of relevant title terms are: investigation-method, alternative-method and in-vitro.

USEFUL TERMS FOR SEARCHING

TOPIC	DESCRIPTOR/CODE
General Topics : Ethics Methods and procedures	Ethics.DE. Commonly posted: Investigation-method.DE.
Replacement Topics : in-vitro in-vivo cell culture physicochemical model mathematical model bacteria fungi insecta alternative method	In-vitro.DE. In-vivo.DE. Tissue-culture.DE., Cell-line.DE., Cell-culture.DE., Established-cell- line.DE. Physicochemical-method.DE., Physicochemical-properties-activity- relationship.DE. Mathematical-model.DE. Bacteria.DE. Fungi.DE. Insect.DE., Insecta.DE. Alternative-method.DE., Replacement.DE.; Substitution.DE.
Reduction Topics : Experimental design Quality control	Experimental-design.DE. Quality-control.DE.
Refinement Topics : Pain Stress Well-being	Pain.DE. Stress.DE. Well-being.DE.; Psychological-well- being.DE.; Physiological wellbeing.DE.

Science Citation Index

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SCOPE OF DATABASE

Coverage: 1974 to date on Dialog and STN; 1980 to date on DataStar
Science Citation Index is a bibliographic database covering international literature in science and technology. It contains c. 19 million references from nearly 6,000 journals covering the full period 1974-Present. It corresponds to the printed Science Citation Index with the addition of records from the Current Contents series that are not included in the print version. Author abstracts are included from 1991.
It covers 11 of our listed 15 core journals.

STRENGTHS & WEAKNESSES

The database has very broad coverage of journals, and the (almost) unique capability of citation searching. It is also possible to display cited references for any document.
Indexing is based on author keywords and 'Keywords Plus' selected from the titles of the cited references. It may be better to exclude the latter from search strategies to avoid unnecessary false drops

USEFUL TERMS FOR SEARCHING

TOPIC	DESCRIPTOR/CODE
General Topics : }	Select appropriate terms from the keywords list and apply as 'Free-text' in the Title, Abstract and Keywords Fields
Replacement Topics : }	
Reduction Topics : }	
Refinement Topics : }	

Toxcenter - ToxFile

NB. In January 2001 the US National Library of Medicine reviewed its database strategy and decided to discontinue TOXLINE. The major database hosts have licensed some of the content and are producing their own versions (summarised below).

Toxcenter

PRODUCER Chemical Abstracts Service
2540 Olentangy River Road
PO Box 3012
Columbus
OH 43210-0012
USA

Website: www.cas.com

SCOPE OF DATABASE

Coverage: 1907 to date on STN

Covers the pharmacological, biochemical, physiological and toxicological effects of drugs and other chemicals. It contains over 5.1 million references, most with abstract and CAS registry numbers. The information is taken from MEDLINE, BIOSIS, Chemical Abstracts and International Pharmaceutical Abstracts. CAS intend to licence other subfiles, formerly included in Toxline.

USEFUL TERMS FOR SEARCHING

Search as for BIOSIS, Chemical Abstracts & MEDLINE. Search across all segments using full-text approach

ToxFile

PRODUCER The Dialog Corporation
11000 Regency Parkway, Suite 10
Cary,
NC 27511
USA

Website: www.dialog.com/

SCOPE OF DATABASE

Coverage: 1966 to date on DataStar and Dialog

Covers information on the toxicological, pharmacological, biochemical and physiological effects of drugs, pesticides and other chemicals. Adverse drug reactions, chemically induced diseases, carcinogenesis, mutagenesis, teratogenesis, environmental pollution, waste disposal, radiation, and food contamination are included. The information is taken from MEDLINE, but Dialog intends to add the 'Toxnet' non-journal subfiles and toxicology records from BIOSIS and International Pharmaceutical Abstracts

USEFUL TERMS FOR SEARCHING

Search as for MEDLINE.

Keywords List

This list covers the main concepts and provides keywords and synonyms encompassed by the topic of alternatives to the use of laboratory animals in biomedical experiments. This includes replacement, reduction and refinement procedures (the 3Rs).

Any consideration of using alternatives to animals or reducing the number used may stem from the ETHICS of using animals in scientific experiments. When considering replacement options, the relevant literature often describes work emphasising methodology (METHODS, PROCEDURES and TECHNIQUES) and the use of human tissue, lower organisms or animal tissue instead of whole animals (TYPES OF STUDY, ORGANISMS). With reduction procedures, the methodology may often relate to MATHEMATICAL AND STATISTICAL PHENOMENA concerned with the design and validation of experiments. When searching for literature on refinement procedures the subject matter frequently relates to ANIMAL WELFARE or to ANIMAL BEHAVIOUR. The keywords and concepts recommended for inclusion under these main concepts are detailed below.

ETHICS

- BIOETHICS
- ANIMAL WELFARE
- ANIMAL RIGHTS
- ANIMAL HUSBANDRY
- ANIMAL TESTING ALTERNATIVE
- ANIMAL TESTING REPLACEMENT
- ANIMAL TESTING REDUCTION
- ANIMAL TESTING REFINEMENT
- HUMANE
- 3RS
- REFINEMENT, REDUCTION AND REPLACEMENT

TYPES OF STUDY

- HUMAN
- ANIMAL
- MAMMAL
- PRIMATE
- NON-PRIMATE
- COMPARATIVE STUDY
- METHODS COMPARISON
- SPECIES COMPARISON
- HUMAN VERSUS ANIMAL COMPARISON
- ANIMAL TESTING ALTERNATIVE
- ANIMAL TESTING REPLACEMENT
- ANIMAL TESTING REDUCTION
- ANIMAL TESTING REFINEMENT
- IN VITRO
- EX VIVO
- ANIMAL CELL
- ANIMAL TISSUE
- HUMAN CELL
- HUMAN TISSUE

ORGAN CULTURE
CELL CULTURE
LEUKOCYTE CULTURE
TUMOR CELL CULTURE
TISSUE CULTURE
CELL LINE
CELL CLONE
IN VIVO
HUMAN EXPERIMENT
ANIMAL EXPERIMENT
CLINICAL STUDY
MODEL
SURROGATE
EXPERIMENTAL MODEL
MOLECULAR MODEL
BIOLOGICAL MODEL
ANIMAL MODEL
DISEASE MODEL
TUMOR MODEL
NON BIOLOGICAL MODEL
COMPUTER MODEL
IN SILICO
CHEMICAL MODEL
PHYSICAL MODEL
PHYSICOCHEMICAL MODEL
MATHEMATICAL MODEL
STATISTICAL MODEL
SIMULATION
DISEASE SIMULATION
COMPUTER SIMULATION
BIOARTIFICIAL
EXPLANT
BIOREACTOR
CADAVER
ORGANOTYPIC
PERFUSED ORGAN

ORGANISMS

INVERTEBRATES
INSECTS
PROTOZOA
HELMINTHS
ALGAE
FUNGI
BACTERIA
PLANTS
MICROORGANISM
NON-PRIMATE

METHODS PROCEDURES AND TECHNIQUES (OR MODELS, SYSTEMS, PROTOCOLS, TESTS, METHODOLOGIES, ASSAYS)

ALTERNATIVE PROCEDURE
ANIMAL TESTING ALTERNATIVE
ANIMAL TESTING REPLACEMENT
ANIMAL TESTING REDUCTION
ANIMAL TESTING REFINEMENT
IN VITRO PROCEDURES
CELL ASSAY

CELL CLONING
CELL LINE
CELL CULTURE
CELL FREE SYSTEM
CELL LYSATE
CELL SUSPENSION
CYTOSOLIC FRACTION
CYTOTOXICITY TESTING
SUBCELLULAR FRACTION
MICROSOMAL PREPARATION
AUTOPSY
BIOPSY
TISSUE CULTURE
TISSUE EXPLANT
TISSUE PREPARATION
TISSUE SLICE
TISSUE EQUIVALENT
IN VITRO EQUIVALENT
ISOLATED ORGAN
ORGAN CULTURE
PERFUSED ORGAN
EMBRYO CULTURE
IN VIVO CULTURE
HOMOGENATE
BLOOD CULTURE
FUNGUS CULTURE
BACTERIUM CULTURE
PARASITE CULTURE
VIRUS CULTURE
COMPUTER TECHNIQUES
COMPUTER MODEL
IN SILICO
COMPUTER SIMULATION
EXPERT SYSTEM
ARTIFICIAL INTELLIGENCE
COMPUTER PREDICTION
PHYSICOCHEMICAL TECHNIQUES
CHEMICAL TECHNIQUES
CHEMICAL MODEL
MOLECULAR MODEL
SAR
QSAR
PHYSICAL TECHNIQUES
PHYSICAL MODEL
MOLECULAR MODEL
MATHEMATICAL TECHNIQUES
THEORETICAL MODEL
MATHEMATICAL MODEL
STATISTICAL MODEL

MATHEMATICAL AND STATISTICAL PHENOMENA

STATISTICS
AVERAGE
CONFIDENCE INTERVALS
CORRELATION
PROBABILITY
PREDICTIVE VALUE OF TESTS
RISK
RELIABILITY

REPRODUCIBILITY
VARIANCE
STATISTICAL ANALYSIS
ANALYSIS OF VARIANCE
MULTIVARIATE ANALYSIS
BIOMETRY
CLUSTER ANALYSIS
REGRESSION ANALYSIS
STATISTICAL DISTRIBUTIONS
BINOMIAL DISTRIBUTION
CHI SQUARE DISTRIBUTION
NORMAL DISTRIBUTION
POISSON DISTRIBUTION
STATISTICAL MODEL
MATHEMATICAL MODEL
CROSSOVER PROCEDURE
DOUBLE BLIND PROCEDURE
METHODS COMPARISON
SPECIES COMPARISON
SINGLE BLIND PROCEDURE
ERROR
QUALITY CONTROL
VALIDATION PROCESS
PREVALIDATION
EXPERIMENTAL DESIGN
SAMPLE SIZE
PARALLEL DESIGN
LATIN SQUARE DESIGN

ANIMAL WELFARE

ANIMAL CARE
ANIMAL USE
ANIMAL RIGHTS
ANIMAL HUSBANDRY
LABORATORY ANIMAL WELFARE
ENVIRONMENTAL ENRICHMENT
ENVIRONMENTAL ENHANCEMENT
PHYSICAL CONSTITUTION
EXERCISE
BODY WEIGHT
WELLBEING
HEALTH STATUS
ACCLIMATISATION
PHYSICAL SENSITIVITY
ENVIRONMENTAL TOLERANCE
ENVIRONMENTAL ACCEPTANCE
STRESS
DISTRESS
PAIN
PAIN PERCEPTION
PAIN MEASUREMENT
PAIN REDUCTION
HUMANE

ANIMAL BEHAVIOUR

ADAPTIVE BEHAVIOUR
EXPLORATORY BEHAVIOUR
AGGRESSION

AVERSION
AVOIDANCE
FEEDING
APPETITE
EATING
DRINKING
MOTOR ACTIVITY
SEXUAL BEHAVIOUR
COPULATION
SOCIAL BEHAVIOUR
NESTING BEHAVIOUR
PREDATORY BEHAVIOUR
GROOMING
ANIMAL COMMUNICATION
VOCALIZATION

Example Generic Search Strategy on Animal Alternatives

When carrying out a search for published literature on animal alternatives in support of an application to the Home Office (or equivalent national regulatory authority) for a project licence, it is suggested that the search is carried out in two stages. The first search can be carried out by combining the topic of interest, such as a specific disease (eg. asthma) or physiological system (eg. skin irritancy), with general alternatives terms (see below). A second search can then be carried out using more specific descriptions of alternative techniques, that can be obtained from the references retrieved by the first search. The references from these two searches can then be combined, and sent to the licence applicant, together with the strategy used and details of the databases searched, for inclusion with the licence application to the Home Office.

The major databases for a search of this type, are: Medline, Biosis, Embase, and SciSearch/Current Contents. These four databases, searched back to 1966*, will normally provide a lot of references. If sufficient references are not retrieved from these 4 databases, then search any/all of the remaining key databases. For certain types of searches it may be necessary to try some of the following specialist databases:

Elsevier Biobase
Biobusiness
Computer Database
JICST
Conference Papers Index
Derwent Veterinary Drug File
Dissertation Abstracts
Biotechnology Abstracts
Bioethicsline
Inspec
Compendex

** Search for references back to 1966, or as far back as the database goes, unless carrying out a search for a licence application which was accompanied previously by animal alternative references retrieved by an information professional search. In the latter case, search back 5-6 years - until the date of the search that accompanied the last licence application, if this is known. As licence applications were not accompanied by literature search references until 2000, this 5 year cycle will not begin until 2005.*

Strategy (DataStar)

- 1) Alternative\$1
- 2) 1.ti.
- 3) Animal\$1 or mammal\$1 or model\$1 or system\$1 or protocol\$1
- 4) Technique\$1 or test\$3 or method\$1 or methodolog\$3 or assay\$1 or procedure\$1
- 5) 1 with (3 or 4)**
- 6) Replac\$6
- 7) 6.ti.
- 8) 6 with (3 or 4)***
- 9) Validat\$3 or Validity or prevalidat\$3
- 10) 9.ti.
- 11) 9 with (3 or 4)
- 12) Vitro
- 13) 12.ti.
- 14) 12 with (1 or 3 or 4)
- 15) 12.so.
- 16) Vivo with (vitro or line\$1 or culture\$1 or explant\$1 or tissue\$1 or bioreactor\$1)
- 17) (model\$4 or simulation) with (cadaver\$1 or computer\$1 or mathematic\$2)
- 18) (Vitro or culture\$1 or line\$1) with (new or novel)
- 19) humane or organotypic or silico or bioartificial
- 20) tissue adj equivalent\$ or vitro adj equivalent\$
- 21) 3Rs.ti,ab,de. or (refin\$6 with replac\$6 with reduc\$5)
- 22) (non or without or exclud\$3 or replac\$6) adj (animal\$1 or mammal\$1) ***
- 23) Cell adj (line\$1 or clone\$)
- 24) ECVAM
- 25) Centre with Validation with Alternative adj Methods
- 26) ICCVAM
- 27) ALTEX.so. or Alternatisen.so.
- 28) AWIC.so
- 29) ATLA.so. or (Alternatives with Animal\$1).so.
- 30) CAAT
- 31) Center with Alternatives with Animal adj Testing
- 32) ERGATT
- 33) European adj Research adj Group with Alternatives with Toxicity adj testing
- 34) IRAG
- 35) Interagency adj Regulatory adj Alternatives adj Group
- 36) 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35

NB. Combine each of the sets, 2, 5, 7, 8, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, and 36, with keywords for the disease/function of interest, then scan the titles of each combined set and print relevant references. If there are too many references, you may need to restrict terms to the title or combine sets with terms/codes for the relevant drug category.

*** Consider searching for any animal species or specific animal test used routinely in the studies of interest, combining the species/test names with the keyword "Alternative(s), or replacement or with terms in set 22"

e.g. Alternative\$1 with (guinea adj pig\$1 or mice or mouse or rat or rats or foot adj pad adj test)

In addition to the above keywords, also use specific Emtree thesaurus terms on Embase:

In-vitro-study#

Cell-culture#

cell-Line#

Tissue-and-organ-preparation-and-culture#

Methodology#

In addition to the above keywords, also use specific MESH thesaurus terms on Medline:

Animal-testing-alternatives

In-vitro.de.

Cells-cultured#

Tissue-culture#

Computer-simulation

MT.DE

In addition to the above keywords, also use specific CONCEPT CODES on Biosis:

32600.CC. and 32500.CC. (codes for "in-vitro" and "tissue culture")

Method code for organ/tissues of interest e.g. Respiratory methods = 16001.CC.

Selected other information sources and further reading

The **FRAME** (Fund for Replacement of Animals in Medical Research) website provides an excellent starting point for information about 3Rs issues, including historical information and legislation, links to electronic journals, information on how to search for alternatives and links to other useful sites.

<http://www.frame.org.uk>

The **Altweb** site also provides a useful collection of 3Rs information. It includes a number of full-text documents such as Russell and Burch's book, 'The Principles of Humane Experimental Technique'. The Altweb search engine enables you to search databases such as Medline, Toxline and Agricola, as well as the Altweb site. It also has an "alternatives" news section and other useful links

<http://altweb.jhsph.edu/>

AWIC Tips for searching for alternatives to animal research and testing

US Animal Welfare Information Center website

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

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(available electronically via FRAME website)
- 3) Smyth D (1978) *Alternatives to Animal Experiments* Scolar Press
- 4) Executive Committee of the Congress (1999) Background to the Three Rs Declaration of Bologna, as Adopted by the 3rd World Congress on Alternatives and Animal use in the Life Sciences, Bologna, Italy, on 31 August 1999 *ATLA* 28 (1) 1-5
- 5) UFAW/FRAME (1998) *Selection and Use of Replacement Methods in Animal Experimentation* UFAW

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