ALTERNATIVE SEARCH DOCUMENTATION

Federal regulations [Title 9, Code of Federal Regulations, Chapter 1, Subchapter A (Animal Welfare), Section 2.31 (d) (ii)] require the IACUC to determine that "The principal investigator has considered alternatives to procedures that may cause more than momentary or slight pain or distress to the animals and has provided a written narrative description of the methods and sources, e.g., the Animal Welfare Information Center, used to determine that alternatives were not available."

1.   What does "alternatives to animal testing" mean when I am doing my research?

Basically, it means considering the 3 Rs when planning research when using animals. The 3Rs are: **Replacement, Reduction,** and **Refinement**.

Replacement is what is usually thought of when one thinks of animal alternatives. Some how, the animal is replaced with a computer model, a lower species of animal, or an in vitro experiment.

Reduction means that the fewest number of animals are used that still produces valid results.

Refinement means that the design inflicts the less amount of pain possible to the animal.

See http://altweb.jhsph.edu/education/FAQs.htm - question02 for more on replacement as well as refinement and reduction.

2.   Why should I consider alternatives to animal testing when planning my research?

1.   **Seeking alternatives to animal testing will ensure compliance with all federal laws, including the Animal Welfare Act (AWA).**

The AWA requires that minimum standards of care and treatment be provided for certain animals bred for commercial sale, used in research, transported commercially, or exhibited to the public. For researchers, this act says they must give regulated animals anesthesia or pain-relieving medication to minimize the pain or distress caused by research if the experiment allows. The AWA also forbids the unnecessary duplication of a specific experiment using regulated animals. For more information on the AWA, see http://www.aphis.usda.gov/oa/pubs/awact.html

Please note, according to the AWA, regulated animals currently does NOT include rats and mice. However, the Public Health Service (PHS) Policy on Humane Care and Use of Laboratory Animals states that for any researcher using PHS funding, they must comply with the AWA even if the species used is not currently covered

under the AWA. Please see http://grants.nih.gov/grants/olaw/references/phspol.htm - intro for more information on the PHS policy.

The regulatory arm of the federal government that enforces the AWA is the Animal and Plant Inspection Service, or APHIS. APHIS has many policies that help them interpret the intent of the AWA and guide them in their work. To see some of these policies used by APHIS, see http://www.aphis.usda.gov/ac/polmanpdf.html

2.   Seeking alternatives to animal testing is also good science and may directly benefit your research.

Researchers who look for alternatives to animal testing can enjoy the following benefits:
1.   Staying current in specific area of research;
2.   Reducing costs in doing research;
3.   Awareness of research from unfamiliar resources or other disciplines;
4.   Reducing duplication in research. (Of course, sometimes replication may be done purposefully, and as such, is good science; otherwise, duplication may jeopardize publication);
5.   Finding opportunities for less painful and invasive procedures;
6.   Finding possible insights to totally new approaches;
7.   Ensuring appropriate numbers of animals will be used;
8.   Identifying possible collaborators for future work;
9.   Reducing stress via proper handling, training, enrichment, group housing, etc. Stressed animals may skew results of experiments.

3.   How can I show I considered alternative methods in my research?
The principal investigators must provide a written narrative of the methods used and sources consulted to determine the availability of alternatives, including refinements, reductions, and replacements. APHIS, in its regulations governing this, states that the performance of a database search remains the most effective and efficient method for demonstrating compliance with the requirement to consider alternatives to painful/distressful procedures. (Please note, a search is not required for an experiment considered Pain Level A). When a database search is the primary means of meeting this requirement, the narrative must, at a minimum, include:

1.   the names of the databases searched;
2.   the date the search was performed;
3.   the period covered by the search; and
4.   the key words and/or the search strategy used.

APHIS does recognize another way for the principal investigators to show compliance. In some circumstances, subject expert consultants may provide relevant and up-to-date information regarding alternatives in lieu of, or in addition to, a database search. For more

information on this APHIS Policy, see http://www.aphis.usda.gov/ac/policy/policy12.pdf

4.   What concepts need to be part of an alternative search?

APHIS, in its Policy 12, ***Consideration of Alternatives to Painful/Distressful Procedures***, specifically mentions The Animal Welfare Information Center (AWIC), an information service of the National Agricultural Library, as the Aexpert@ in information about alternatives. In its role as expert and to help IACUCs, investigators, and animal research support people understand the alternatives section of the regulations, AWIC staff developed a two-day workshop called "Meeting the Information Requirements of the Animal Welfare Act." The workshop provides an overview of the Animal Welfare Act looking specifically at the information requirements.

In this workshop, several characteristics of a good alternative search are mentioned:

1.   The search is done prior to, or in conjunction with, the development of the research protocol.

2.   More than one database is searched. Just searching Medline, for example, may not adequately cover all the literature out there on a topic.

3.   The search goes back at least five years, or more, depending on the topic.

4.   The search adequately explores the following questions:

   1.   Duplication:
           Does this research duplicate previously reported research? Duplication is specifically mentioned as not allowed under the AWA.

   2.   Reduction:
           Have all attempts to reduce the number of animals used been explored? Similar reported research may discuss novel statistical methods that may allow the use of smaller number of animals.

   3.   Refinement:
           1.   Does the proposed protocol consider state-of-the-art thinking on husbandry for the animals? This includes such things as caging, handling, responsible monitoring of the animal, as well as consideration of humane treatment and reduction of pain and distress of the animal.

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2.   Are less invasive and less painful procedures available?

3.   Are anesthesia and analgesics proposed and are they adequate for
the procedures proposed and the species proposed? Are there more
effective means for use of these agents?

2.   Replacement:
Have all non-animal models, either partial replacement or total
replacement models, been considered? Has lower organism models, either
partial replacement or total replacements models, been considered?

Please note, these above concepts are taken directly from the APHIS= Policy 12,
Consideration of Alternatives to Painful/Distressful Procedures.

5.   What would a model alternative search look like?

Let=s show an example. A researcher is interested in evaluating telithromycin, a member
of a new class of antibiotics called ketolides, against experimental otitis media infection
due to penicillin resistant Streptococcus pneumoniae (PRSP) and Haemophilus influenzae
(NTHI). The species proposed is the chinchilla (Chinchilla sp.). Procedures proposed
include cardiac puncture for blood collection, anesthesia, and surgery for middle ear
(bullae) fluid collection.

NB - There is no Aone@ way to do a literature search. Below is simply one example following the principles listed above.

a.   To cover the concepts for ***Duplication and Reduction***, the following strategy
might be used. Below the strategy, see some of the titles of the articles retrieved.
Not all may be relevant but certainly, some titles are worth investigating by the
researcher.

Database: BIOSIS, Current Contents, Pre-MEDLINE, MEDLINE
Search Strategy:
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1   ((otitis adj1 media) or (ear adj3 infect$)).mp. [mp=ti, kw, hw, rw, ab, bc, bt, bo, dz, sh, kp]
(18959)
2   (streptococc$ or haemophil$ or prsp or nthi).mp. [mp=ti, kw, hw, rw, ab, bc, bt, bo, dz, sh, kp]
(143110)
3   (antibiotic$ or ketolide$ or telithromycin).mp. [mp=ti, kw, hw, rw, ab, bc, bt, bo, dz, sh, kp]
(304077)
4   1 and 2 and 3 (1401)
5   chinchilla.mp. [mp=ti, kw, hw, rw, ab, bc, bt, bo, dz, sh, kp] (3893)

6   4 and 5 (32)

7   from 6 keep 1-32 (32)

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S   A new rat model of otitis media caused by Streptococcus pneumoniae: Conditions and application in immunization protocols

S   An experimental study of cefixime in the treatment of Streptococcus pneumoniae otitis media.

S   An experimental model for measuring middle ear antimicrobial drug penetration in otitis media.

S   Efficacy of clarithromycin treatment of acute otitis media caused by infection with penicillin-susceptible, -intermediate, and -resistant Streptococcus pneumoniae in the chinchilla.

S   Efficacy of clarithromycin treatment of acute otitis media caused by infection with penicillin-susceptible, -intermediate, and -resistant Streptococcus pneumoniae in the chinchilla.

S   Efficacy of linezolid in experimental otitis media

S   Experimental otitis media in chinchillas.

S   Experimental animal models for studying antimicrobial pharmacokinetics in otitis media.

S   HYDROLASE ACTIVITY IN MIDDLE EAR EFFUSIONS EFFECT OF ANTIBIOTIC THERAPY.

S   Longitudinal study of the efficacy of ampicillin in the treatment of pneumococcal otitis media in a chinchilla animal model.

S   Monitoring pH of otitis media effusion in chinchillas using fluorescence spectroscopy.

S   Nasopharyngeal colonization with nontypeable Haemophilus influenzae in chinchillas.

S   PCR-based detection of bacterial DNA after antimicrobial treatment is indicative of persistent, viable bacteria in the chinchilla model of otitis media.

S   Penicillin treatment accelerates middle ear inflammation in experimental pneumococcal otitis media.

S   Permeability of the normal round window membrane to Haemophilus influenzae type b endotoxin.

S   Recurrent pneumococcal otitis media in the chinchilla (Chinchilla laniger).

S   Recurrent pneumococcal otitis media in the chinchilla. A longitudinal study.

S   The effect of antibiotic treatment on the release of endotoxin during nontypable Haemophilus influenzae-induced otitis media in the chinchilla.

S   Third-generation cephalosporins in the treatment of acute pneumococcal otitis media. An animal study.

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2.   To cover all aspects of *Refinement* (different procedures or less painful ways of doing procedures, husbandry and use of anesthesia) the following three search strategies may be used. Following each strategy are the titles of articles that were received using that strategy. Again, while all may not be relevant, some are worthwhile the researcher investigating.

Database: BIOSIS, Current Contents, Pre-MEDLINE, MEDLINE
Search Strategy:
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1   (chinchilla not (chinchilla adj1 (rat or rats or rabbit$))).mp. [mp=ti, kw, hw, rw, ab, bc, bt, bo, dz, sh, kp] (2770)
2   ((otitis adj1 media) or (middle adj1 ear) or (ear adj3 infect$)).mp. [mp=ti, kw, hw, rw, ab, bc, bt, bo, dz, sh, kp] (30560)
3   (fluid$ or culture$ or bullae).mp. [mp=ti, kw, hw, rw, ab, bc, bt, bo, dz, sh, kp] (1548320)
4   2 and 3 (3698)
5   (blood adj1 (collect$ or remov$ or sample$ or withdraw$)).mp. [mp=ti, kw, hw, rw, ab, bc, bt, bo, dz, sh, kp] (116944)
6   (cardiac adj1 puncture$).mp. [mp=ti, kw, hw, rw, ab, bc, bt, bo, dz, sh, kp] (661)
7   4 or 5 or 6 (120954)
8   1 and 7 (226)
9   remove duplicates from 8 (137)
10   from 9 keep 1-137 (137)

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S   A SIMPLE METHOD FOR INTRAVENOUS INJECTION AND BLOOD
         COLLECTION IN THE CHINCHILLA CHINCHILLA-LANIGER.
S   A new rat model of otitis media caused by Streptococcus pneumoniae: Conditions and
         application in immunization protocols
S   ADHERENCE OF NON-TYPEABLE HAEMOPHILUS INFLUENZAE PROMOTES
         REORGANIZATION OF THE ACTIN CYTOSKELETON IN HUMAN OR
         CHINCHILLA EPITHELIAL CELLS IN VITRO
S   Comparison of two otitis media models for the study of middle ear antimicrobial
         pharmacokinetics.
S   Effect of adenovirus type 1 and influenza A virus on Streptococcus pneumoniae
         nasopharyngeal colonization and otitis media in the chinchilla.
S   Effect of platelet activating factor and its antagonist on the mucociliary clearance of the
         eustachian tube in guinea pigs
S   Efficacy of ceftibuten for acute otitis media caused by Haemophilus influenzae: An
         animal study.
S   EICOSANOID SYNTHESIS AND INACTIVATION IN HEALTHY AND INFECTED
         CHINCHILLA MIDDLE EARS
S   Evidence for transudation of specific antibody into the middle ear parenterally immunized
         chinchillas after an upper respiratory tract infection with adenovirus.
S   EXPERIMENTAL ANIMAL MODELS FOR STUDYING ANTIMICROBIAL
         PHARMACOKINETICS IN OTITIS MEDIA.
S   Fimbria-mediated enhanced attachment of nontypeable Haemophilus influenzae to
         respiratory syncytial virus-infected respiratory epithelial cells
S   Influenza A virus infection of human middle ear cells in vitro
S   Juvenile keratin inoculation induces chronic ear pathology.
S   MIDDLE EAR FLUID LYSOZYME SOURCE IN EXPERIMENTAL
         PNEUMOCOCCAL OTITIS MEDIA.
S   MODELING ADENOVIRUS TYPE 1-INDUCED OTITIS MEDIA IN THE
         CHINCHILLA - EFFECT ON CILIARY ACTIVITY AND FLUID TRANSPORT
         FUNCTION OF EUSTACHIAN TUBE MUCOSAL EPITHELIUM (VOL 168, PG 865,
         1993)
S   Otitis media: The chinchilla model.

S   Recurrent pneumococcal otitis media in the chinchilla (Chinchilla laniger).

S   RELATIONSHIP BETWEEN ANTIGEN LEVELS IN MIDDLE EAR AND ANTIGEN PASSAGE THROUGH ROUND WINDOW MEMBRANE IN ANTIGEN-INDUCED OTITIS MEDIA.

S   SERIAL CULTURE AND CHARACTERIZATION OF THE CHINCHILLA MIDDLE EAR EPITHELIUM.

S   THE ACYLATED FORM OF PROTEIN D OF HAEMOPHILUS INFLUENZAE IS MORE IMMUNOGENIC THAN THE NONACYLATED FORM AND ELICITS AN ADJUVANT EFFECT WHEN IT IS USED AS A CARRIER CONJUGATED TO POLYRIBOSYL RIBITOL PHOSPHATE

S   Time of Penicillin Treatment Influences the Course of Streptococcus pneumoniae-Induced Middle Ear Inflammation.

Database: BIOSIS, Current Contents, Pre-MEDLINE, MEDLINE
Search Strategy:
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1   (chinchilla not (chinchilla adj1 (rat or rats or rabbit$))).mp. [mp=ti, kw, hw, rw, ab, bc, bt, bo, dz, sh, kp] (2770)
2   caging.ti. (210)
3   cage$.ti. (6596)
4   humane.ti. (609)
5   handl$.ti. (13184)
6   hous$.ti. (40052)
7   welfare.ti. (9954)
8   distress.ti. (14652)
9   pain.ti. (81411)
10   monitor$.ti. (88690)
11   observ$.ti. (126818)
12   2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 (379693)
13   1 and 12 (22)
14   remove duplicates from 13 (20)
15   from 14 keep 1-20 (20)

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Note : No citations have been listed that would have resulted from the above search.

Database: BIOSIS, Current Contents, Pre-MEDLINE, MEDLINE
Search Strategy:
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1   (chinchilla not (chinchilla adj1 (rat or rats or rabbit$))).mp. [mp=ti, kw, hw, rw, ab, bc, bt, bo, dz, sh, kp] (2770)
2   anesthesia.ti. (44761)
3   anaesthesia.ti. (18618)
4   analgesci$.ti. (1)
5   2 or 3 or 4 (63376)

6   1 and 5 (3)
7   remove duplicates from 6 (1)
8   from 7 keep 1 (1)

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The effects of anesthesia on otoacoustic emissions.

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24.   To cover the concepts for ***Replacement***, the following strategy might be used.

Database: BIOSIS, Current Contents, Pre-MEDLINE, MEDLINE
Search Strategy:
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1   ((otitis adj1 media) or (ear adj3 infect$)).mp. [mp=ti, kw, hw, rw, ab, bc, bt, bo, dz, sh, kp]
(18959)
2   (streptococc$ or haemophil$ or prsp or nthi).mp. [mp=ti, kw, hw, rw, ab, bc, bt, bo, dz, sh, kp]
(143110)
3   (antibiotic$ or ketolide$ or telithromycin).mp. [mp=ti, kw, hw, rw, ab, bc, bt, bo, dz, sh, kp]
(304077)
4   1 and 2 and 3 (1401)
5   alternative.ti. (44129)
6   (animal adj1 test$).ti. (454)
7   model$.ti. (444566)
8   simulation$.ti. (58944)
9   tissue$.ti. (258934)
10   culture$.ti. (270079)
11   vitro.ti. (290125)
12   method$.ti. (411922)
13   5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (1691624)
14   4 and 13 (72)
15   remove duplicates from 14 (48)
16   from 15 keep 1-48 (48)

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S   A GERBIL MODEL FOR RHOMBENCEPHALITIS DUE TO LISTERIA
       MONOCYTOGENES
S   A new rat model of otitis media caused by Streptococcus pneumoniae: conditions and
       application in immunization protocols.
S   An experimental model for measuring middle ear antimicrobial drug penetration in otitis
       media.
S   An in vitro pharmacodynamic model to simulate antibiotic behavior of acute otitis media
       with effusion.
S   Antibiotics and return visits for respiratory illness: A comparison of pooled versus
       hierarchical statistical methods
S   Attachment of Streptococcus pneumoniae to human pharyngeal epithelial cells in vitro.
S   Azithromycin: The first of the tissue-selective azalides.
S   Correlation of nasopharyngeal and conjunctival cultures with middle ear fluid cultures in

otitis media. A prospective study.

S   Current in vitro sensitivity of the most frequent bacterial respiratory pathogens: clinical implications [Spanish]

S   Disparate cultures of middle ear fluids. Results from children with bilateral otitis media.

S   EPIDEMIOLOGY AND IN VITRO SUSCEPTIBILITY OF DRUG-RESISTANT STREPTOCOCCUS PNEUMONIAE

S   Experimental animal models for studying antimicrobial pharmacokinetics in otitis media.

S   Haemophilus influenzae in otitis media and sinusitis: serotypes and susceptibilty to ampicillin and amoxycillin in vitro.

S   Hemophilus influenzae type B soft tissue infections of the head and neck. [Review] [28 refs]

S   Histopathology of experimental acute otitis media caused by various bacteria an investigation on goblet cell density, polyp- and adhesion formation, bone modeling dynamics and the effect of antibiotic treatment [Review]

S   Immunization and protection in pneumococcal otitis media studied in a rat model. [Review] [37 refs]

S   Improved detection of Streptococcus pneumoniae in middle-ear fluid cultures by use of a gentamicin-containing medium

S   In vitro activity of novel fluoroquinolones against Streptococcus pneumoniae isolated from children with acute otitis media.

S   In vitro development of resistance to ceftriaxone, cefprozil and azithromycin in Streptococcus pneumoniae.

S   In vitro activities of the oxazolidinone compounds linezolid (PNU-100766) and eperzolid (PNU-100592) against middle ear isolates of Streptococcus pneumoniae

S   In vitro response of bacteria found as etiological agents in otitis media in childhood. [Turkish]

S   In vitro activity and pharmacodynamics of oral beta-lactam antibiotics against Streptococcus pneumoniae from southeast Missouri.

S   In vitro activity of antibiotics commonly used in the treatment of otitis media against Streptococcus pneumoniae isolates with different susceptibilities to penicillin.

S   In vitro susceptibility of upper respiratory tract pathogens to 13 oral antimicrobial agents.

S   In-vitro activity of cefprozil (BMY 28100) and loracarbef (LY 163892) against pathogens obtained from middle ear fluid.

S   In-vitro bactericidal activity of four oral antibiotics against pathogens responsible for acute otitis media in children.

S   In vivo efficacies of amoxicillin and cefuroxime against penicillin-resistant Streptococcus pneumoniae in a gerbil model of acute otitis media.

S   IN VITRO ACTIVITIES OF ORAL BETA-LACTAMS AT CONCENTRATIONS ACHIEVED IN HUMANS AGAINST PENICILLIN-SUSCEPTIBLE AND -RESISTANT PNEUMOCOCCI AND POTENTIAL TO SELECT RESISTANCE

S   Indication-based use of antimicrobials in Finnish primary health care - Description of a method for data collection and results of its application

S   Limiting the spread of resistant pneumococci: Biological and epidemiologic evidence for the effectiveness of alternative interventions [Review]

S   Longitudinal study of the efficacy of ampicillin in the treatment of pneumococcal otitis media in a chinchilla animal model.

S   Methods for decreasing antibiotic use in otitis media.

S   PCR-based detection of bacterial DNA after antimicrobial treatment is indicative of persistent, viable bacteria in the chinchilla model of otitis media.

S   Pharmacokinetic and in vivo studies with azithromycin (CP-62,993), a new macrolide

                with an extended half-life and excellent tissue distribution.

S   Pharmacokinetic and pharmacodynamic parameters for antimicrobial effects of cefotaxime and amoxicillin in an in vitro kinetic model

S   Predictive value of pneumococcal nasopharyngeal cultures for the assessment of nonresponsive acute otitis media in children.

S   RATIONALE BEHIND HIGH-DOSE AMOXICILLIN THERAPY FOR ACUTE OTITIS MEDIA DUE TO PENICILLIN-NONSUSCEPTIBLE PNEUMOCOCCI - SUPPORT FROM IN VITRO PHARMACODYNAMIC STUDIES

S   Review of in vitro activity, pharmacokinetic characteristics, safety, and clinical efficacy of cefprozil, a new oral cephalosporin. [Review] [43 refs]

S   Role of Streptococcus pneumoniae and Haemophilus influenzae in the development of acute otitis media and otitis media with effusion in a gerbil model.

S   Sinus tissue pharmacokinetics after oral administration of amoxicillin/clavulanic acid.

S   Streptococcus pneumoniae in the USA: in vitro susceptibility and pharmacodynamic analysis

S   The correlation of in vitro tests with the outcome of antimicrobial therapy for otitis media.

S   Tissue concentrations of ofloxacin in the middle ear.

S   Tissue expander infections in children: look beyond the expander pocket.

S   USE OF GAS LIQUID CHROMATOGRAPHY AS AN ADJUNCT TO CONVENTIONAL BACTERIOLOGICAL METHODS IN THE DIAGNOSIS OF ANAEROBIC CEREBRAL ABSCESS.

S   Wound contamination and antimicrobial susceptibility of bacteria cultured during total ear canal ablation and lateral bulla osteotomy in dogs.

6.   Where can I find help?

The professional staff at the Health Sciences Library would be happy to do the search for alternatives for animal testing for UMKC researchers. A draft copy of the IACUC protocol forms would be the best information to provide for the searches to be done.

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