

Accessing Information on the Reduction, Refinement and Replacement of Animal Experiments

Report and Recommendations of a Focus on Alternatives Workshop

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Introduction

All scientists who use animals in scientific procedures have an ethical obligation to ensure that the research aims cannot be achieved in other ways. However, in many countries, including those of the European Union, this responsibility is also a legislative requirement (1, 2).

Finding and using information about the use of the Three Rs (reduction, refinement and replacement; 3) in animal procedures should be an integral part of any research project, to help to minimise animal use and suffering, and to facilitate good scientific practice. Every individual involved in animal experiments should constantly question the use of animals and make every effort to implement all aspects of the Three Rs. Other groups, such as research funding bodies, regulatory bodies and animal protection organisations, also need to access information about the Three Rs.

However, reliable and up-to-date information about the Three Rs can be difficult to

locate and retrieve. A workshop organised by the European Centre for the Validation of Alternative Methods (ECVAM, EC Joint Research Centre, Ispra, Italy) reviewed existing information resources on alternatives, and called for a clearer understanding of the needs of users (4).

Focus on Alternatives, a group of British organisations working together to advance the replacement of animal experiments, held a workshop in London, UK, on 3 September 1998 to assess the effectiveness of existing information on the Three Rs, and to identify what is lacking and how it could be provided. The workshop, *Accessing Information on Alternatives: Discussing the Case for a New Resource*, was attended by 34 participants, including information technologists, scientists from academia and industry, representatives of government regulatory bodies and research-funding agencies, animal protection societies, humane research groups and other non-governmental organisations.

This report is intended to inform and promote discussion about accessing information

on the Three Rs. It is hoped that it will help to improve existing information facilities, and to identify what new resources might be required.

Legislative Requirements in Europe

European *Directive 86/609/EEC* (1) requires that non-animal alternatives to animal experiments are used wherever possible (replacement), that the number of animals should be minimised (reduction), and that the smallest degree of pain and distress is caused to animals used for justifiable purposes (refinement).

The Directive is implemented in Europe through national legislation; for example, in Britain, the relevant law is the *Animals (Scientific Procedures) Act 1986* (2). The British Home Office Inspectorate plays a fundamental role in implementing the 1986 Act, especially in advising the Secretary of State on whether project licences for animal procedures should be granted. Researchers applying for project licences are expected to incorporate all aspects of the Three Rs in the planning, design and conduct of their work on animals.

From 1 April 1999, mandatory ethical review processes will be in place in every British establishment where animals are bred or supplied for, or used in, scientific procedures. These ethical review processes are expected to improve the scientific and animal welfare aspects of project licence applications, and will address reduction, refinement and replacement. An additional new control is that researchers applying to the Home Office for project licences to use animals will be required to detail precisely what consideration they have given to implementing the Three Rs in their proposed studies.

Clearly, fulfilling the requirements of European and national legislation depends on the availability of up-to-date and comprehensive information about the Three Rs. The Home Office Inspectorate has identified several limitations with existing resources (see below). The Inspectorate is developing its own in-house databases on policy, study design, key references to animal models and the Three Rs, but, for reasons of confidentiality, it is unable to make this information generally available.

Information Resources Currently Used

In their search for information about the Three Rs, individuals use a range of information resources to varying extents. Most of the workshop participants use major databases such as MEDLINE and TOXLINE to search for information on reduction, refinement and replacement. The limitations of these databases are discussed below.

Other participants use Internet Web sites, including those of the Animal Welfare Information Center (AWIC), the Center for Alternatives to Animal Testing (the CAAT Web site is called Altweb), and FRAME. A list of relevant Web sites and databases is given in Table I. Journals which specialise in non-animal methods, such as *ATLA* and *In Vitro Toxicology*, primarily focus on toxicology; biomedical researchers looking for other information on the Three Rs are less well-served by specialist journals.

Research-funding bodies tend to seek information on the Three Rs by consulting experts known to them through their peer-review systems. They also use the BIOETHICSLINE and AWIC Web sites. The latter site provides useful information on how to conduct a computer search to obtain details on the Three Rs.

Representatives from animal protection and humane research groups consult FRAME or ECVAM or their publications, the Web sites of CAAT and the Universities Federation for Animal Welfare (UFAW), or the MEDLINE, NORINA, *INVITTOX* or in-house databases. The British Library relies mainly on MEDLINE.

Not all users are aware of the potential of Internet discussion groups, which could be a useful means of exchanging expertise in the Three Rs.

Problems with Current Resources

A number of difficulties were identified with existing information resources, although these were experienced to varying degrees.

Searching for information

Major databases such as TOXLINE and MEDLINE are not considered to be useful sources of information about the Three Rs, and many scientists do not regularly

Table I: Databases and Web sites containing information on the Three Rs

Web site/database	Address
Altweb (CAAT)	http://altweb.jhsph.edu/
AWIC	http://www.nal.usda.gov/awic/awic.htm
BIOETHICSLINE	http://igm.nlm.nih.gov
BIOSIS	http://www.biosis.org/
DIMDI	http://gripsdb.dimdi.de/engl/usercode.htm
ECVAM	http://www.ei.jrc.it/report/ecvam.html
FRAME	http://www.frame-uk.demon.co.uk
Infotrieve	http://www.infotrieve.com
INVITTOX	INVITTOX, 96–98 North Sherwood Street, Nottingham NG1 4EE, UK
MEDLINE	http://www.ncbi.nlm.nih.gov/PubMed/
NORINA	http://netvet.wustl.edu/norina.htm
TOXLINE	http://igm.nlm.nih.gov
UFAW	http://www.ufaw3.dircon.co.uk

search them. These databases are very large, and do not deal specifically with the reduction, refinement and replacement of animal experiments. Consequently, a considerable amount of irrelevant material retrieved in a search must be discarded before the desired information can be identified — if at all.

The relevant search terms used by existing bibliographic databases, such as MEDLINE's "animal testing alternatives", are insufficient. Conducting a useful search may require significant time and skill, and even then can fail to provide the information required. Moreover, many potential users feel they lack the expertise to retrieve the information they want and do not have access to an information specialist.

While some databases can be accessed and searched simultaneously from a single entry point, this sometimes requires payment of a subscription. Other databases need to be searched separately. A fee might also be charged for some of these.

The process of searching the Internet for a specialist Web site on the Three Rs, and expanding outwards to other sites embedded in the first site, can be very slow. Expert networking via the Internet might be useful, although assessing the quality of information provided by other participants can be difficult.

Incomplete information

The current scientific databases do not adequately cover the Three Rs, and most are not tailored for searches on these topics. Moreover, major databases such as MEDLINE are solely bibliographical, and do not provide other types of information. For these reasons, some scientists are not confident that their searches will be comprehensive. The *INVITTOX* database provides details of *in vitro* toxicity testing protocols, but is not accessible on the Internet. Due to resource limitations, there are sometimes delays before new methods are available from *INVITTOX*.

As well as information about replacement alternatives, details of reduction and refinement (of both procedures and husbandry) are essential. Most animal users seek more in-depth information about experimental protocols to help them refine their projects (for instance, by developing a more humane endpoint), and to reduce the number of animals required. However, as stated by the Home Office Chief Inspector, important methodological "tricks of the trade", as well as problems encountered, lessons learned and refinements achieved, are often not published in papers. This deficiency, together with the fact that published papers are not indexed by method,

means that existing databases are difficult to use for finding information on the least severe protocols.

Proposed Solutions

Ideally, information resources should be accessible at any time, comprehensive, up-to-date, reliable, cheap and user-friendly.

Training and guidance on sources and searching

Students and scientists should receive wider training in the Three Rs and in information retrieval and evaluation. Specific training and guidance on database search strategies for the Three Rs is considered essential for those conducting animal procedures, and might also be welcomed by information providers.

Later this year, the FRAME Web site will contain guidance notes on the use of search engines and on setting up search strategies. It will have links to information on the Three Rs and details of electronic discussion groups, and will be updated regularly.

To ensure that searches are comprehensive, the workshop participants considered that a generic decision strategy would be helpful, especially if it was available on the Internet. The strategy, possibly in the form of a flow chart or a decision tree, should not be prescriptive, but should provide guidance on the essential steps scientists should take to ensure they have not overlooked any aspect of the Three Rs. Members of Focus on Alternatives are hoping to develop such a decision tree.

For each search, the results of every step would be recorded, which would provide an "audit trail" to demonstrate (for example, to institutional and national regulatory authorities) that adequate consideration has been given to reducing, refining and replacing animal procedures. Over time, each establishment might be able to develop a body of data relevant to its research interests, which would be used to inform future licence applicants.

The information technologists at the workshop recommended that specialist information providers, where available, should always be involved in a search and could help with interpretation. Most company-based researchers are satisfied with the assistance

given by their information providers, but other users do not have access to such specialists, or are reluctant to rely on them entirely.

In Britain, mandatory training courses for new project licensees include information on the Three Rs. However, the content is variable and is seldom comprehensive. Moreover, scientists who held project licences before training courses became mandatory might not have the necessary expertise. They should be required to undertake training in finding information on, and implementing, the Three Rs. All project licensees should have access to regular updates on information facilities and techniques. A training officer should also visit establishments to advise on information resources and on how best to use them.

Improving existing resources

Ideally, existing databases such as MEDLINE, EMBASE and BIOSIS would include the Three Rs terminology in their indexing systems. However, the information specialists felt it would be difficult to persuade the major databases to restructure their systems; moreover, any changes to indexing policies would not be retrospective.

Journal editors and publishers could ask their authors to use relevant keywords and to mention the Three Rs in their abstracts. Additionally, journal referees could be asked to highlight whether the work they are reviewing has a bearing on the Three Rs. If one or two influential journals could be persuaded to adopt this approach, others might follow. In this respect, the workshop participants agreed with many of the recommendations made during discussions at the 2nd World Congress on Alternatives and Animal Use in the Life Sciences (5).

Journals could also be encouraged to expand their coverage of methodology and protocols, either in their printed copies or in their electronic editions on the Internet. A number of initiatives are being developed in this area.

Centralised access to databases

The workshop participants agreed that interrogating several databases simultaneously by a central access service or super-search facility would be advantageous. Some of the broad-field biomedical databases can already

be accessed in this way. For example, PREX is a database host operated by Utrecht University. An annual fee permits access to up to four major bibliographic databases of the life sciences plus 12–15 core databases, some of which offer limited information about alternatives. Subscribers conduct their own searches. Another super-search system is provided by DIMDI, located in Germany, which permits simultaneous searching of a large number of databases.

Another approach to centralised information resources was suggested during the workshop on databases held by ECVAM (4). An international Central Reference Point could be established to provide comprehensive specialist assistance to all those seeking information and advice about the Three Rs. At the moment, however, a global service of this kind is beyond the capabilities of any one organisation. A more modest, national service which would conduct database searches for a fee might be an attractive option, if user costs were kept low.

New databases

Existing major databases are unlikely to expand their coverage of the Three Rs, and a new, single, comprehensive Three Rs database does not appear to be a feasible proposition. The ECVAM workshop suggested that a number of databases and information services, providing for various needs, would be required (4).

The participants at the Focus on Alternatives workshop generally agreed that a selection of smaller, comprehensive databases, each clearly focused on a defined aspect of the Three Rs for a specific purpose, would be the best approach. One current example is the NORINA database of audiovisual facilities which can reduce or replace animal use in education. NORINA is available on the Internet free of charge.

ECVAM is creating some specialist databases. These include a closed-access database providing information on validation studies and the validation status of various methods. Another database, still at an early stage of development, will provide full descriptions of non-animal techniques in toxicology, including protocols. A third database will be bibliographic, and a fourth will list laboratories working in the field of *in vitro* toxicology. The intention is that, ultimately, most of

these databases will be accessible to users worldwide.

The ECVAM databases are still at an early stage of development, and they focus predominantly on *in vitro* toxicology. Replacement methods in biomedical research (as distinct from toxicology), as well as reduction and refinement, are notably under-represented in existing and in planned databases.

The British Library is developing a proposal for a new database of non-animal research sponsored by humane research organisations around the world. It would include biomedical research and would be established and run by the British Library. However, external funding is required.

Targeted information and specialist networking

Information resources which target a specific field or technology (for example, cancer research, genetic engineering) were considered potentially valuable. These could take the form of newsletters, e-mails, specialist databases, on-line discussion groups, or even a contact list of experts. A regular e-mail update (which could be sent to all designated establishments on a disk for internal e-mailing) or a simple printed newsletter for photocopying in-house, could be an effective way of keeping up-to-date with developments in the Three Rs. Updates need to appear either on individuals' desks or on their computer screens; putting a newsletter in the library is unlikely to be effective.

Regular updates of targeted information can be obtained from some databases on the Internet. For example, the database host Infotrieve can be used to search MEDLINE or TOXLINE for alternatives to eye irritation testing, and references to subsequent publications on this topic can be requested from Infotrieve at regular intervals via e-mail. However, the usefulness of these databases is limited, as they do not adequately address the Three Rs.

The workshop participants were interested in specialist on-line discussion forums, which give subscribers an opportunity to ask questions of other members and to respond to queries. An early attempt to run an electronic discussion group about alternatives, called Altanim, was not entirely successful, possibly because it covered too many fields and was not well publicised. Now that the Internet and e-mail are more widely used,

several specialist groups, each with a narrower focus, might be more effective. Those interested could establish new forums to discuss reduction, refinement or replacement in their own fields.

The quality of information provided by other participants in electronic discussion groups could be assessed by asking discussants to provide their *curricula vitae*, or by pursuing a topic in more detail with a participant. For commercial users for whom confidentiality is important, access could be restricted to known experts. With e-mail lists, the discussion can be kept on the topic (for example, the replacement of animal procedures) by using a moderator who only forwards relevant e-mails to discussants.

There are already some specialist groups for project licence holders (under the British *Animals [Scientific Procedures] Act 1986*). CompMed and RatTalk are other electronic discussion forums which touch on the Three Rs occasionally. Not all of the workshop participants were aware of existing on-line discussion groups which might be of interest. An updated review of relevant groups will be available on the FRAME Web site guidance document.

Role of the Home Office

Several participants felt that the in-house information on the Three Rs acquired by the British Home Office would be of use to researchers and others. The Home Office does try to identify and disseminate best practice. For example, "minimum severity protocols" have been published for some standard procedures, as has guidance on other issues such as the use of neuromuscular blocking agents. However, it is limited by resources and confidentiality constraints.

The workshop participants felt that the Home Office could be more active in providing information, perhaps by including updates on the Three Rs in their regular mailings to senior personnel (certificate holders) at animal breeding, supplying and user establishments.

Conclusions and Recommendations

1. Every individual involved in animal experimentation should take personal

responsibility for implementing the reduction, refinement and replacement of animal procedures at all stages of their work.

2. Finding and using information about the Three Rs should be an integral part of any research project, ensuring high welfare standards for animals, minimal animal suffering, a reduction in animal numbers, and best scientific practice.
3. Training courses for new licence holders in Britain should include more-comprehensive information about the Three Rs, and it should be mandatory for all licensees, both new and established, to attend such courses.
4. On-going training and guidance in the Three Rs, and in how to use information resources, are considered essential. These could take the form of training courses, visiting training officers, a dedicated Web site, or even a booklet or newsletter, as long as it was widely circulated.
5. Researchers in establishments which have information experts are encouraged to seek their assistance and advice. Information providers might themselves benefit from specialist training in the Three Rs.
6. A generic decision-making strategy would be helpful to ensure that a comprehensive search for the Three Rs is made. The strategy, perhaps in the form of a flow chart, could provide guidance on the basic steps which a researcher should take. This might also form the framework for an "audit trail", which could be submitted to institutional ethical review processes and to national authorities which licence animal procedures. A guidance document which will assist in conducting a search will be available on the FRAME Web site later in 1999.
7. Existing information resources on the Three Rs are limited, and improved opportunities to access more-extensive data are required. In particular, specialist information on the Three Rs in biomedical research (as opposed to toxicology) is not readily available from the existing databases. The new data-

bases planned by ECVAM are almost exclusively toxicological, so there is a serious shortfall of information in the wide field of biomedical research.

8. Existing databases, such as MEDLINE, are unlikely to significantly expand their coverage of the Three Rs. A new, all-encompassing database is probably impractical. The most realistic approach is to establish several specialist, relatively small-scale databases dealing with complementary aspects of the Three Rs.
9. The new databases should be accessible by a super-search facility, permitting users to interrogate all relevant databases simultaneously. Another potentially useful facility would be a professional, centralised service which would conduct searches on behalf of users. In both cases, costs should be kept to a minimum to facilitate widespread use.
10. New on-line discussion groups offer an inexpensive and accessible way of sharing specialist knowledge about the Three Rs.
11. Publishers and editors of scientific journals should be encouraged to request their authors and referees to highlight aspects of published work which are rel-

evant to the Three Rs. Editors should also be urged to expand on useful methodologies, in printed and/or electronic editions.

12. Regular updates of developments in the Three Rs and information resources about them, possibly in the form of e-mails or newsletters, would also be useful for individuals.

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