

National Competent Authorities for the implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes

A working document on the Availability of Information on the Three Rs

Brussels, 29-30 November 2012

The Commission convened an Expert Working Group (EWG) to investigate practical ways in which the obligation for application of the Three Rs, as required by Directive 2010/63/EU, can be fully realised, and to provide guidance covering Three R information sources, communication exchange, and information sharing for the benefit of those involved in the care and use of animals for scientific purposes. All Member States and main stakeholder organisations were invited to nominate experts to participate in the work.

This document is the result of the work of the EWG meeting, discussions with the Member States as well as legal input from the Commission. It was endorsed by the National Competent Authorities for the implementation of Directive 2010/63/EU at their meeting of 18-19 September 2013.

It is hoped that the specific recommendations will be taken up by those concerned; some will be followed up by the Commission. This document aims at covering comprehensively all elements discussed at the EWG, providing a list of reference sources and recommendations supported by the EWG as well as highlighting areas of difficulty to be examined further in more detail in the future.

Disclaimer:

The following is intended as guidance to assist the Member States and others affected by Directive 2010/63/EU on the protection of animals used for scientific purposes to arrive at a common understanding of the provisions contained in the Directive and to facilitate its implementation. All comments should be considered within the context of this Directive 2010/63/EU. It provides some suggestions on how the requirements of the Directive may be met. The content of the document does not impose additional obligations beyond those laid out in the Directive.

Only the Court of Justice of the European Union is entitled to interpret EU law with legally binding authority.

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Article 1(1) – Subject matter and scope

1(1) *This Directive establishes measures for the protection of animals used for scientific or educational purposes. To that end, it lays down rules on the following:*

*(a) the **replacement** and **reduction** of the use of animals in procedures and the **refinement** of the breeding, accommodation, care and use of animals in procedures;*

...

Article 4 - Principle of replacement, reduction and refinement

1. *Member States shall ensure that, wherever possible, a scientifically satisfactory method or testing strategy, not entailing the use of live animals, shall be used instead of a procedure [= a method using animals].*

2. *Member States shall ensure that the number of animals used in projects is reduced to a minimum without compromising the objectives of the project.*

3. *Member States shall ensure refinement of breeding, accommodation and care, and of methods used in procedures, eliminating or reducing to the minimum any possible pain, suffering, distress or lasting harm to the animals.*

4. *This Article shall, in the choice of methods, be implemented in accordance with Article 13.*

Article 47 - Alternative approaches

47(4) *Member States shall, at national level, ensure the promotion of alternative approaches and the dissemination of information thereon.*

47(6) *Commission shall take appropriate action with a view to obtaining international acceptance of alternative approaches validated in the Union.*

Article 49 – National committees for the protection of animals used for scientific purposes

49(1) *Each Member State shall establish a national committee for the protection of animals used for scientific purposes. It shall advise the competent authorities and animal-welfare bodies on matters dealing with the acquisition, breeding, accommodation, care and use of animals in procedures and ensure sharing of best practice.*

49(2) *The national committees referred to in paragraph 1 shall exchange information on the operation of animal-welfare bodies and project evaluation and share best practice within the Union.*

In addition to these specific requirements, the Directive contains obligations for a number of specific roles, the fulfilment of which requires either access to the latest information on the Three Rs or dissemination of information on the Three Rs to enable others to comply with their obligations.

Executive summary

The National Contact Points of the Member States responsible for the implementation of Directive 2010/63/EU on the protection of animals used for scientific purposes and stakeholders were tasked by the Commission with investigating practical ways in which the obligation for application of the Three Rs can be fully realised, and ultimately assist the Commission in providing guidance covering Three R information sources, communication exchange, information sharing etc. to those involved in the use of animals for scientific purposes.

Information, be it on any area in which new developments take place continuously, is never static. The environment of data sources as well as key players are constantly evolving with new players and tools appearing while existing ones disappear, are superseded or are no longer maintained. This makes it particularly challenging to ensure that the latest information on the Three Rs reaches the right audiences, in the right format and at the right time.

To achieve these goals

- Education and training of personnel involved in the care and use of animals should include guidance on how and where to search, obtain and share up-to-date information on the Three Rs.
- All those with responsibilities under the Directive need to keep up to date on Three Rs developments and promote and apply their uptake as appropriate within their establishment.
- Systems should be in place from information providers to ensure that information is easily accessible, regularly updated and relevant information disseminated to appropriate personnel. This may be facilitated within an establishment by the person responsible for ensuring staff have access to relevant information, and by the Animal Welfare Body. National Committees should consider how to ensure information on the Three Rs is best made available, perhaps through a national centre or repository.
- Although there are extensive databases on alternatives, particularly in the field of toxicology and other safety evaluations, information on the remaining two Rs (Reduction and Refinement) should be further developed. Similarly, improved databases for Three Rs within fundamental research would be helpful.
- Information on new developments and applications of the Three Rs should be more widely available, and scientific publications and funding bodies should be encouraged to report these.

Objectives

Ensuring implementation of the Three Rs is a key requirement of the Directive. Persons involved in the use and care of animals are responsible for ensuring that the Three Rs are effectively applied – access to appropriate and up-to-date information is a pre-requisite. To meet these expectations, it is essential that all involved have a clear understanding of their role, and have the tools and means to access the necessary information on the Three Rs to enable them to fulfil their role.

The objectives of this document are to

1. Clarify the roles of the key named persons under the Directive as facilitators of the application and implementation of Three Rs;
2. Consider how to increase awareness and understanding of the information sources available on the Three Rs and how best to search for and within these;
3. Develop an understanding of the responsibilities of different persons as a source for, or as a receiver of information and the obligation to disseminate Three Rs information at all levels from global to European as well as at national, regional, local, establishment and individual level.

It is also important to identify areas of difficulty as well as best practice in accessing and disseminating information on the Three Rs, and to develop recommendations to facilitate application of the Three Rs and compliance with the Directive.

Areas given consideration in the development of this document included

- How to identify available sources of information;
- How to increase awareness and understanding of information sources on the Three Rs and the available search tools;
- How to ensure that all relevant Three Rs information is obtained and that such information is up to date;
- Identifying areas of difficulty as well as best practice in accessing and disseminating information on the Three Rs;
- Developing recommendations in relation to Three Rs information;
- Clarifying the obligations of each different role as a source of or a receiver of information;
- Developing recommendations to improve information flow for specific roles;
- Identifying other important stakeholders that can play a role in improving information exchange.

Roles in the Directive as a source, or a user, of information on the Three Rs

The following roles are identified in the Directive which either have a need to access information or are in a position to disseminate information on the Three Rs:

- Article 20(2) – the person responsible for compliance with the Directive;
- Art 23 – individuals designing projects, carrying out procedures on, caring for and killing animals, including scientist/researchers disseminating results of the work;
- Art 24(1)(a) – the person responsible for the welfare and care of the animals in an establishment;
- Art 24(1)(b)(c) – the person(s) responsible for the access to information and for education, training and competence of personnel;
- Art 25 – designated veterinarians;
- Art 26 – members of an animal welfare body;
- Art 34 – inspectors;
- Art 38, Art 59 - the competent authority (persons responsible) for project evaluations;
- Art 39 – the competent authority (persons responsible) for retrospective assessments;
- Art 47 - PARERE contact person;
- Art 49 – the members of a National Committee for the protection of animals used for scientific purposes;
- Educators involved in teaching Three Rs.

Other players have important roles in the dissemination of information on the Three Rs including

- regulatory authorities at national, European and international level;
- other stakeholders (NGOs, function / profession specific organisations such as those for veterinarians and laboratory animal technologists and laboratory animal science associations).

Further obligations and responsibilities under Directive 2010/63/EU

- Art 47 – sets requirements for Member States on the Three Rs and the development and validation of alternative approaches;
- Art 24 - training and continuous professional development (CPD) requirements on the Three Rs.

Raising awareness on available information sources

Today, the use of web-based tools to search for information is the norm. There are a number of organisations providing portals to different information sources as well as producing guidance on the Three Rs. However, it is imperative to recognise that these sources are constantly evolving with new ones becoming available while others do not remain current.

With this recognition comes the responsibility for those who need Three Rs information to be pro-active in keeping themselves up-to date, and to ensure that the information acquired truly presents the most up-to-date in the field.

Data sources include:

- Databases on the Three Rs (generic or research/field specific)
- Information portals, web-sites (including regulatory authorities at national, European and international level)
- Journals
- Webinars
- Conferences
- Study days
- Central repositories such as national and international Three Rs Centres
- Personal networks
- Individual organisations

Data sources are listed in Appendix I. These links are also provided in the Commission web-site (under sub-menu "Key resources") at

http://ec.europa.eu/environment/chemicals/lab_animals/3r/alternatives_information_en.htm

Databases and other data sources - problems and issues

- Databases – The main problems encountered are access, suitability (identification of which is most appropriate for the need) and ensuring the information is up-to-date (which can be facilitated by the inclusion of a 'last updated' date on the database).
- Fees for use can restrict access for many people to databases or the full articles held within them e.g. MEDLINE Database.
- Databases mainly cover safety and regulatory testing areas, or other specific areas, e.g. DB-ALM.
- There is a need for more and improved databases on Three Rs application in the areas of basic research and translational research. The view was expressed that there is poorer communication of Three Rs and dissemination of information in these areas than in the regulatory field.
- There are a number of databases relating to alternatives in regulatory testing, which has led to some duplication. This makes it difficult for the user to understand which data source should be prioritised and/or which is most up-to-date, as some are not well maintained.
- Restricted access to proprietary data in the area of regulatory testing is problematic.

- The amount of data obtained in database searches can be overwhelming which can make it very difficult to identify which is most relevant for the individual searching for information.
- Information obtained should be meaningful and relevant – which is difficult to obtain without appropriate training and suitable search strategies.
- Lack of standardization of the provided information makes comparison difficult.
- Languages can create a barrier – not all information is available in more than one language, and not all words easily translate.
- Using inappropriate search criteria can result in inappropriate or incomplete search results.
- Literature/Systematic Review - a level of expertise is required in a review of the literature; a systematic review is generally much more extensive but can be very time-consuming.

Databases and other data sources – solutions and recommendations

- Database providers should
 - ensure suitable profile and awareness within scientific community and provide clear narratives on the contents, structure, scope and potential uses of the respective databases;
 - provide open access;
 - offer automated update alerts and/or notification emails for new updates and newly added validated methods;
 - indicate review/update dates.
- All those involved with dissemination of information should improve visibility of key databases / search engines which are found to be useful – a link to these through the European Commission website should be considered.
- The European Commission should ensure free access to all EU Framework Programme sponsored project results, ideally from a single access point.
- The provision of quality controlled information by databases is required. Information contained in them should have undergone quality review.
- Signposts to databases and journals are needed – these could be developed and listed by national Three Rs Centres.

- Journals should be a key tool for dissemination amongst scientists – the level of focus on Three Rs elements needs to be raised among the publishing community.
- Publication of "negative results" (studies for which the hypotheses are not proven) should become norm for all journals – equally, publication of unexpected experimental problems is important to prevent recurrence.
- Establishments should encourage project applicants to make available search results for project applications to minimise duplication of work and as reference for others.

Data sources in the area of regulatory testing

Animal testing is still required in a number of areas for regulatory purposes to assess the safety and/or efficacy of the substances/products. These include areas such as pharmaceuticals, vaccines, medical devices, chemicals, biocides, plant protection products, food safety, food contact material etc.

Accessing information on the Three Rs in these areas is facilitated by the fact that methods are often described in the legislation (and/or guidance), and these are applicable to a specific, clearly defined area. This enables structuring of databases and specific search tools.

The problems in this area include

- proprietary issues - it is not always possible to find out who owns the data or gain access to it;
- the exchange of Three Rs information can be prohibited by competition laws;
- lack of cooperation in some areas of regulatory testing leading to different requirements by different regulatory bodies;
- the costs of obtaining information on test requirements/alternative methods can be prohibitive (e.g. Monographs maintained by EDQM European Pharmacopoeia);
- in some areas too much information is available, often in an unstructured and poorly accessible format, making it difficult to find and select 'the right data';
- regulatory requirements may substantially differ between different geographical regions.

Two regulatory areas are illustrated below as examples of how to explore different data sources and the associated issues and solutions:

Regulatory testing: Example Pharmaceuticals/Biologicals – [The European Directorate for the Quality of Medicines and HealthCare \(EDQM\), directorate of the Council of Europe](#), is the body responsible for the European Pharmacopoeia which represents, through its monographs and general methods the official harmonised quality standard for pharmaceutical products within the respective signatory parties to the European Pharmacopoeia Convention. It actively promotes and disseminates information

through its website, Three Rs Conferences and training programmes. The EDQM website includes a specific page on alternatives to animal testing (<http://www.edqm.eu/en/Alternatives-to-animal-testing-1483.html>). All studies in the field of the Three Rs are reported in Pharmeuropa, Pharmeuropa Bio and scientific notes which are available free of charge (<http://www.edqm.eu/en/pharmeuropa-bio-and-scientific-notes-584.html>).
[<http://www.edqm.eu/en/Alternatives-to-animal-testing-1483.html>]

Regulatory testing: Example Chemicals – EU Chemicals legislation ([REACH](#)) requires information on the chemical substances and their safety. In some cases, the information can only be obtained through animal testing. Testing on vertebrate animals for the purpose of REACH shall be undertaken only as a last resort. Test methods are described in a [Test Method Regulation](#) following closely the international OECD Test Method Guidelines. Registrants of chemical substances should collect all information possible (e.g. from QSARs, read-across from other substances, *in vitro* testing, epidemiological data) which would allow avoidance of animal testing. Guidance on how alternative approaches can be used is available from the [European Chemicals Agency \(ECHA\)](#).
[<http://echa.europa.eu/web/guest/guidance-documents/guidance-on-information-requirements-and-chemical-safety-assessment>]

European Union Reference Laboratory for alternatives to animal testing (EURL ECVAM) has made available a tracking system to enable the development of alternative methods to be followed.

The [EURL ECVAM Tracking System on Alternative methods towards Regulatory acceptance \(TSAR\)](#) is a tool aimed at providing a transparent view on the status of alternative methods as they progress from purely scientific protocols submitted for eventual validation to being actively used in a regulatory context. This tracking system intends to cover all steps, from the initial submission for validation until final adoption by inclusion in the EU legislation and/or related Guidance Documents, when appropriate.
[<http://tsar.jrc.ec.europa.eu/>]

EURL ECVAM also provides a database on alternative methods.

The [EURL ECVAM DataBase service on ALternative Methods \(DB-ALM\)](#) includes a collection of data-sets providing *factual* information (not only bibliographic references) presented as *evaluated* (and therefore *ready-to-use*) data sheets. It provides an overall picture on the state-of-the-art of alternative methods for a given topic area in the form of method summary descriptions and/or more detailed information, such as protocols and results to allow the transfer and use of a method by a laboratory. Current focus is given to toxicology, but is not limited to it. [<http://ecvam-dbalm.jrc.ec.europa.eu/>]

Data sources in the area of regulatory testing – solutions and recommendations

- Currently there is much focus on toxicology, and not enough information on other areas such as biologicals, medical devices. The authorities responsible for issuing regulatory requirements on the use of animals in all areas should increase efforts in the dissemination of easily accessible, non-fee-attached information on the latest developments on the Three Rs in their respective areas.
- Existing databases on the application of all Three Rs should be expanded to all areas of regulatory use of animals.
- Information on alternative approaches, even if sufficient, is often spread among different legislative requirements making it difficult for the user to locate it. Information on the Three Rs should be easily accessible and clearly indicated in the respective web-sites. The establishment of a portal providing easy access the specialised databases in the various areas would be advisable.
- Information exchange is crucial. Regulatory authorities and industry should establish tools for identifying and disseminating information on new applications of the Three Rs in the regulatory context, and in Refinement specifically in areas where Replacement methods are not envisaged with the current scientific knowledge.
- Industry initiatives to co-operate in areas of non-IP related Three Rs projects should be supported and the results thereof made publicly available and disseminated widely.
- Publication on Refinement methods in the area of regulatory use of animals through scientific journals should be encouraged. This will require better consideration of what goes into section for descriptions of the studies as well as supportive journal editorial policies.

Raising awareness on available search tools and methodologies

Information on available search tools is made available through a number of channels including:

- Through initial, continuing and refresher education and training (see recommendations under section "Improving access to information through education and training")
- By the person responsible for ensuring access to information within an establishment (Article 24(1)(b))
- By Animal Welfare Bodies / National Committees
- By Professional organisations

- Through journals / newsletters

Systematic Review/Meta-analysis of animal models: A Systematic Review (SR) is a thorough, systematic analysis of earlier conducted and published experiments. These form the basis of evidence-based medicine and are already standard practice for clinical studies. The use of SRs for the optimisation of animal testing is however still rare. This is surprising considering these studies constitute the basis of new clinical studies, including the decision whether new treatment methods are also suitable for humans.

- [SYstematic Review Centre for Laboratory animal Experimentation, SYRCLE](#), is a research group of the Central Animal Laboratory of the Radboud University Nijmegen Medical Centre providing guide and search facilities for Systematic Review/Meta-analysis of animal models.
- SYRCLE encourages the use of SRs in animal studies as they improve scientific quality and prevent unnecessary duplication of animal studies and unnecessary animal use, leading to a reduction in animal use.
- A systematic review is focused on a single question which tries to identify, appraise, select and synthesise all available high-quality research evidence relevant to this question. A specifically defined search method is used and more than one database needs to be consulted before the known steps for clinical research can be taken. This approach allows for the quality of scientific results to be assessed. [<http://www.syrcle.nl/>]

Examples of search tools are included in Appendix I.

Search tools - problems and issues

- Most search tools have a special focus on regulatory toxicity and safety testing.
- Some search tools are time consuming to use – the benefit to the scientist of the time they are investing is not always obvious at outset.
- Applications of the Three Rs appropriate for different animal models will not be identified unless correct search terms are used. Similarly, such differences between animal models will only be identified in searches if the terms are explicitly mentioned by the authors of the respective documents. Specific search strategies remain to be developed to allow a more detailed interrogation /sub-group analysis that can identify such differences.
- A systematic approach to carrying out a search is often lacking.
- The Project Evaluation process should give consideration to the appropriateness of the searches undertaken on the Three Rs.

Search tools – solutions and recommendations

- Search tools should be further developed to provide an in-depth coverage of areas other than regulatory safety and toxicology.
- Harmonisation of systematic approaches to a search (e.g. use of search terms or keywords) should be encouraged and their use reported in scientific publications.
- Establishment and systematic use of 'search checklists' should be encouraged for those required to search for information on the Three Rs. Finding already published animal studies becomes easier and gives a more complete result by using already existing search filters, such as those for Embase and Pubmed e.g.:
<http://www.ncbi.nlm.nih.gov/pubmed/20551243>;
<http://www.ncbi.nlm.nih.gov/pubmed/23836850>;
<http://www.ncbi.nlm.nih.gov/pubmed/21890653>.
- Introduce a 'Good Practice' for data retrievals approaches into training courses for scientists, senior welfare and care staff, designated veterinarians and those responsible for information availability in the establishment and those conducting project evaluations. Create awareness and include the use of search tools and data sources as part of standard Three Rs training¹
- Include awareness and use of harmonised reporting through guidelines on publications e.g. ARRIVE guidelines (see Appendix II) in the training for scientists.

Roles and responsibilities: an effective network for communication and co-ordination

The Directive requires that personnel involved in the care and use of animals are trained and competent to perform their tasks. There is also an obligation to apply the Three Rs in the breeding, accommodation, care and use of animals.

An effective network within an establishment is necessary to ensure that all necessary information is available to those caring and using animals. Such a network will include information providers, such as the person named in Article 24(1)(b), training and care staff and those responsible for designing and carrying out procedures.

A number of presentations are available on the Commission web-site http://ec.europa.eu/environment/chemicals/lab_animals/3r/alternatives_information_en.htm

which identify challenges and approaches taken **by those with roles under the Directive** to overcome these, to facilitate the accessing and dissemination of information within establishments.

¹ http://ec.europa.eu/environment/chemicals/lab_animals/pdf/Endorsed_E-T.pdf

The main issues identified and recommendations addressing these to ensure effective co-ordination and dissemination of information include:

- A clear definition of responsibilities and expectations for each role under the Directive, as regards the provision and dissemination of information on the Three Rs, is needed at establishment level¹.
- All persons should be pro-active in ensuring that they have all the relevant information they need to fulfil their role, and where appropriate they should also ensure that other persons have access to relevant information to discharge their own responsibilities.
- National Committees under Article 49 have an important role to promote and disseminate information on Three Rs. This should be clearly described including established channels of communication, and made publicly available.
- Good communication among those with different roles, in particular inspectors and evaluators, is essential. Poor communication was identified as a key block to the dissemination of information within establishments.
- There should be strategies and structures in place to ensure information on new, innovative applications of Three Rs is made widely and rapidly available.
- Animal caretakers and technologists and veterinarians should be incorporated in formal discussions and exchange on application of the Three Rs; from project conception to completion and follow-up.
- Staying up-to-date with the latest developments on the Three Rs may carry a cost in terms of personnel time and resources. However, as it is a legal requirement of the Directive to implement the Three Rs, management should ensure sufficient time is made available for this, and the Three Rs benefits to both animal welfare and science are emphasised.
- Certain roles under the Directive require that newly acquired data are distributed for appropriate audiences and utilised.
 - For example: members of Animal Welfare Body, person(s) responsible for the welfare and care of animals, the designated veterinarian, the training and competency, and the information persons all have a role to play. Their role is to increase awareness and constantly review and promote improved standards and practices within establishments.
 - As these roles may vary slightly from one establishment to another, it is recommended that the establishments clarify each of these functions in respect to their role as the disseminator of the Three Rs information, with whom they interact and the channels to be used.

- Information flow should be top down, bottom up and regular. Information should be kept current, by regular review, and application of any appropriate recommendations should be ensured.
- A creation of a central national repository for Three R information, such as National Three Rs centre should be supported. This could be part of a National Committee's role.
- Inspectors can also have a proactive role as advisors and promoters of the latest Three Rs information.

Improving access to information through education and training

To ensure that all persons involved in the use and care of animals are fully informed on the available information on the Three Rs, initial education and training for such personnel should include an introduction to the sourcing and utilisation of 3Rs information relevant to their responsibilities.

- Standard teaching materials and methods need to reflect Three Rs requirements – in addition to teaching the application of Three Rs, the learning outcomes should also cover a 'Good Practice' for data retrieval approaches including information resources, tools for search practices, methods of analysis and reporting.
- Attitudes towards implementing new Three Rs techniques may be entrenched and some people may be reluctant to embrace change. To address this, the role of education and training in creating the right attitude should be recognised and exploited.
- Teachers and Three 3Rs teaching materials need to stay up-to-date.
- Availability of, and access to, good teaching material should be facilitated through closer collaboration at both European and internal level.²
- Those persons applying for, or evaluating, or carrying out work under proposed projects should be provided with appropriate training on sourcing information on Three Rs starting early in the educational career.³
- A variety of channels of can be used for dissemination of information on the Three Rs through CPD such as :
 - Study days – for information exchange and to remain current;
 - Webinars –useful for information exchange;

² http://ec.europa.eu/environment/chemicals/lab_animals/pdf/Endorsed_E-T.pdf

- Use of the available experience of colleagues: e.g. a good scientist can educate others on Three Rs.
- A specific area of the EC website should be developed for information on Education and Training.
- Education and training should promote the publication of Three Rs developments in journals. All scientists, journals and funding bodies should follow structured publishing guidelines, containing all relevant information on the design and care of animals, such as the ARRIVE guidelines.

General recommendations

In addition to clarifying roles and responsibilities, establishing effective networks of communication and ensuring appropriate education and training from the start, promotion, encouragement and guidance is seen as part of the solution. General recommendations include:

- Three Rs prizes should be offered at all levels – including in the area of dissemination of Three Rs information and not, as at present, only on innovative applications.
- The use of structured publishing guidelines such as the ARRIVE guidelines by journals/grant awarding bodies will encourage scientists to focus more effort on reporting on the Three Rs.
- Funding bodies should stress that they expect the Three Rs to be fully implemented, and demand good practice including obligatory publication of results irrespective of the study outcome.
- Publicity is the key for Three R information. Use of fora such as the World Congress on Alternatives to Animal Testing, along with other large mainstream scientific meetings to disseminate information should be encouraged.
- Use of the EC website to provide links to Three Rs information sites and portals should increase visibility.
- Evidence of the search strategy for Three Rs relevant to each project, and when it was carried out, should be included in all project applications.
- The Commission should produce guidance on the project application process. For example, the application form needs to ask the right questions, and steer people in right direction.³

³ http://ec.europa.eu/environment/chemicals/lab_animals/pdf/Endorsed_PE-RA.pdf

- Outreach towards those conducting basic research is needed, and encouragement to researchers to investigate Three Rs possibilities, highlighting the benefits of such an approach. There should be continuous push for scientists to look at research conducted at other establishments, and in other countries.

Although there are various frameworks in place for searching for Three Rs information, there remain some areas of concern. Member States and other stakeholders should as necessary take action to fill gaps, improve access where necessary and confirm that appropriate searches have been undertaken to ensure all opportunities for implementation of the Three Rs have been identified.

Appendix I

Additional information sources on the Three Rs

Information Portals

- [NC3Rs: National Centre for Three Rs, UK](http://www.nc3rs.org.uk/) – a mainly government funded body which provides input to the UK’s Three Rs agenda, carries out research and provides funds for Three R research. [<http://www.nc3rs.org.uk/>]
- [CAAT-Europe \(Centre of Alternatives to Animal Testing\)](http://cms.uni-konstanz.de/leist/caat-europe/) – an academic, science based centre within the John Hopkins Bloomberg School of Public Health in the USA and the University of Konstanz in Germany which is dedicated to the promotion of research into *in vitro* and other alternative techniques, Three Rs education and information. [<http://cms.uni-konstanz.de/leist/caat-europe/>]
- [CCAC- Canadian Council on Animal Care](http://ccac.ca/) – promotes the application of Three Rs in Canada. Through a website it provides the latest information on the Three Rs, a search tool and a search guide. [<http://ccac.ca/>]
- The [EURL ECVAM Tracking System on Alternative methods towards Regulatory acceptance \(TSAR\)](http://tsar.jrc.ec.europa.eu/) is a tool aimed at providing a transparent view on the status of alternative methods as they progress from purely scientific protocols submitted for eventual validation to being actively used in a regulatory context. This tracking system intends to cover all steps, from the initial submission for validation until final adoption by inclusion in the EU legislation and/or related Guidance Documents, when appropriate.
[<http://tsar.jrc.ec.europa.eu/>]

Search Tools

- [EURL ECVAM ECVAM Search Guide \(the Guide\)](#) – The Guide is particularly helpful to inexperienced database users. It represents a useful resource where comprehensive searches for alternatives are required as part of authorisation processes for animal experiments and where regulatory requirements mandate the application of the Three Rs. The Guide provides examples of search procedures and user guidance to facilitate the location of the desired information on Three Rs alternatives; it also includes an inventory of relevant resources, contains a check list (the seven golden steps) to allow for searches in a structured and systematic manner, moreover, search principles, suggested search terms etc. Free copies of the handbook or a pdf version

are available from the [EU Bookshop](#).

[<http://bookshop.europa.eu/en/the-eurl-ecvam-search-guide-pbLBN124391/>]

- **[Go3R](#)** - is a free of charge 'semantic' search engine making use of underlying expert knowledge on 3Rs methods to specifically retrieve Three Rs-relevant information. Currently, the semantic Go3R tool searches in the databases PubMed and TOXNET. Additionally, Go3R allows searching the entire World Wide Web using a Google search with automatic higher ranking of 3Rs relevant websites. Results of PubMed and TOXNET searches are presented to the user together with a dynamic table of contents highlighting 3Rs information and allowing to quickly restrict vast search results to relevant documents. The Go3R expert knowledge covers the entire scientific domain of alternatives to animal testing in all biomedical disciplines, but has a special focus on regulatory toxicity testing. [www.Go3R.org]

Databases

[AnimAlt-ZEBET database](#) - the database of the Zentralstelle zur Erfassung und Bewertung von Ersatz- und Ergänzungsmethoden zum Tierversuch, is a full-text database of evaluated alternative methods to animal experiments in biomedicine and related fields. All documents are evaluated from the '3-Rs' concept. Sources are approx. 800 different books, journals, and monographs, laws, regulations, directions, guidelines, recommendations, pharmacopoea, dissertations, congress papers, proceedings of meetings, conferences, and symposia. The method number, method title, keywords, evaluation, abstract and bibliographic references are searchable. [<http://www.dimdi.de/static/en/db/dbinfo/zt00.htm>]

[EMBASE from Elsevier Life Science Solutions](#) is an international database for biomedical researchers. It enables to track and retrieve precise information on drugs and diseases from pre-clinical studies to searches on critical toxicological information. It covers over 25 million indexed records from thousands of peer-reviewed journals. [<http://www.embase.com/>]

[The EURL ECVAM DataBase service on ALternative Methods \(DB-ALM\)](#) includes a collection of data-sets providing factual information (not only bibliographic references) presented as evaluated (and therefore ready-to-use) data sheets. It provides an overall picture on the state-of-the-art of alternative methods for a given topic area in the form of method summary descriptions and/or more detailed information, such as protocols and results to allow the transfer and use of a method by a laboratory. Current focus is given to toxicology, but is not limited to it. [<http://ecvam-dbalm.jrc.ec.europa.eu/>]

[EURL ECVAM QSAR Model Inventory of the Commission's Joint Research Centre \(JRC\)](#) contains information on the validity of (Q)SAR models that have been submitted to the JRC. The database is intended to help to identify valid (Q)SARs, e.g. for the purposes of REACH. For the description of the models an internationally

standardised Model Reporting Format (QMRF) is used providing key information on (Q)SAR models, including the results of any validation studies. The information is structured according to the OECD principles for the validation of (Q)SAR models. [http://ihcp.jrc.ec.europa.eu/our_databases/jrc-qsar-inventory]

[Europe PubMed Central \(Europe PMC\)](#) is a full-text article database offering free access to biomedical literature resources such as PubMed abstracts, Europe PMC full text articles, Patent abstracts, NHS clinical guidelines, Agricola records and Chinese Biological Abstracts. It is supported by 26 funders of life sciences and biomedical research, including charities and government organisations across Europe, led by the Wellcome Trust. Europe PMC is developed by the European Bioinformatics Institute, The University of Manchester and the British Library. [<http://europepmc.org/>]

[NORINA \(A Norwegian Inventory of Audiovisuals\)](#) is a database with search engine on the website. It contains audiovisual aids that can be used to replace or supplement the use of animals or animal material in teaching and training at all levels from schools to University. It contains at present information on 3,900 products, classified into 23 categories (e.g. anatomy, physiology) and 24 types (e.g. computer program, model). It covers all Three Rs, is in English and free of charge. [<http://oslovet.norecopa.no/NORINA>]

[PubMed](#) comprises more than 22 million citations for biomedical literature from MEDLINE, life science journals, and online books. Citations may include links to full-text content from PubMed Central and publisher web sites. Abstracts contained in PubMed are free of charge, however, a cost is usually associated with the full articles. [<http://www.ncbi.nlm.nih.gov/pubmed/>]

[TextBase](#) is a database with search engine on website. It provides description of textbooks and other written material within Laboratory Animal Science. It includes also textbooks and hand-outs on dissections. It can be used as a resource by researchers and staff at a laboratory animal facility when planning or conducting animal experiments. The dissection manuals in TextBase can be used as guides to dissection or as replacements. It contains at present information on 1,500 products, searchable by free text, title, author, publication year or publisher. It covers all Three Rs, is in English and free of charge. [http://oslovet.norecopa.no/fag.aspx?fag=58&mnu=databases_2]

[Toxicology Data Network](#) contains 14 databases on toxicology, hazardous chemicals, environmental health, and toxic releases hosted by US National Library of Medicine. [<http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?index.html>]

[Web of knowledge](#), part of Web of Science, hosted by Thomson Reuters provides a single destination to access the most reliable, integrated, multidisciplinary research. Quality, curated content delivered alongside information on emerging trends, subject specific content and analysis tools make it easy for students, faculty, researchers, analysts, and program managers to pinpoint the most relevant research to inform their

work. It provides information from data, books, journals, proceedings or patents.
[<http://apps.webofknowledge.com/>]

Journals

The list of [AGRICOLA and Veterinary Science Journals](#) are maintained by the United States Agricultural Information Network. It is an organization for information professionals that provides a forum for discussion of agricultural issues, takes a leadership role in the formation of a national information policy as related to agriculture, makes recommendations to the National Agricultural Library on agricultural information matters, and promotes cooperation and communication among its members. [<http://usain.org/AGRICOLA/vetscience.html>]

[ALTEX](#), edited by the Swiss Society ALTEX Edition, is the official journal of CAAT (the Johns Hopkins Center for Alternatives to Animal Testing), EUSAAT (the European Society for Alternatives to Animal Testing), t4, the Transatlantic Think Tank for Toxicology (Baltimore, Utrecht, Konstanz), and the Doerenkamp chairs in Germany, India, The Netherlands, Switzerland, and USA. ALTEX is devoted to the publication of research on the development and promotion of alternatives to animal experiments. [<http://altweb.jhsph.edu/altex/>]

[Animal Welfare](#) is an international scientific and technical journal. It publishes the results of peer-reviewed scientific research, technical studies and reviews. Generally, papers published in Animal Welfare are not available as 'open access' (available free to all) but through subscription to UFAW or 'pay per view' However, arrangements can be made for open access publication of papers where authors prefer this. [www.ufaw.org.uk/animal.php]

[Applied Animal Behaviour Science](#) is an international journal reporting on the application of ethology to animals managed by humans.
[www.journals.elsevier.com/applied-animal-behaviour-science/]

[Laboratory Animals](#) is an international journal of laboratory animal science and welfare. Laboratory Animals publishes peer-reviewed original papers and reviews on all aspects of the use of animals in biomedical research. The journal promotes improvements in the welfare or well-being of the animals used, it particularly focuses on research that reduces the number of animals used or which replaces animal models with in vitro alternatives. [<http://la.rsmjournals.com/>]

[PLOS](#) is a non-profit organization and publishes [seven peer-reviewed open-access journals](#). They include PLOS ONE, which publishes all rigorous science across the full range of life and health sciences; the community journals (PLOS Genetics, PLOS Computational Biology, PLOS Pathogens, and PLOS Neglected Tropical Diseases); and PLOS Medicine and PLOS Biology. PLOS journals also welcome publication of studies that did not prove the hypotheses (so called 'negative results').
[<http://www.plos.org/>]

Portals – web-sites

[Animal Welfare Information Centre \(AWIC\)](http://awic.nal.usda.gov/) is part of the US Department of Agriculture. It is mandated by the Animal Welfare Act (AWA) to provide information for improved animal care and use in research, testing, teaching, and exhibition. [<http://awic.nal.usda.gov/>]

[Alternatives to Animal Testing](http://altweb.jhsph.edu/) web site was created to serve as a gateway to alternatives news, information, and resources on the Internet and beyond. Altweb hosts the journal ALTEX: Alternatives to Animal Experimentation, which is the official publication of the Johns Hopkins Center for Alternatives to Animal Testing (CAAT). [<http://altweb.jhsph.edu/>]

[Bibliography on Alternatives to Animal Testing \(Altbib\)](http://toxnet.nlm.nih.gov/altbib.html), is a resource portal for Alternatives to the Use of Live Vertebrates in Biomedical Research and Testing hosted by Specialized Information Services of US National Library of Medicine. [<http://toxnet.nlm.nih.gov/altbib.html>]

[Fund for the Replacement of Animals in Medical Experiments \(FRAME\)](http://www.frame.org.uk/) is dedicated to the development of new and valid methods that will replace the need for laboratory animals in medical and scientific research, education, and testing. Where the use of animals is currently necessary, FRAME supports the reduction of numbers involved to an unavoidable minimum and refinement of experimental procedures to minimise any suffering caused. **[The E-learning resource](#)** of FRAME has been set up to provide teachers, school children, students and general supporters with information about the different areas of animal experimentation and with specific resources as to how it can be **[reduced](#)**, **[refined](#)** or **[replaced](#)**. [<http://www.frame.org.uk/>]

[http://www.3Rs-reduction.co.uk](http://www.3rs-reduction.co.uk) – is a new interactive web-site designed to help scientists to improve the design of their animal experiments. Animal experiments are not always well designed, leading to both ethical concerns and a waste of scientific resources. This is a world-wide problem. Training scientists is difficult as there so are few statisticians with a good understanding of laboratory animal science able to provide such training. This new web-site is designed to help scientists to teach themselves the necessary skills. After an introduction on the ethics of animal experimentation, showing that improvements are needed, it goes on to cover choice of experimental units, avoiding bias, power and sample size, controlling variability, types of experimental design, factorial experiments, statistical analysis and publication guidelines. Most sections are followed by a "Test yourself" page of true/false questions. The web-site is free. [<http://www.3rs-reduction.co.uk/>]

[InVitro Jobs](#) - The aim of "InVitroJobs" is to enable researchers to access this branch of research more easily. Alongside the job search portal, the site maintains an up-to-date list of research groups active in the development of animal-free techniques. The primary aims of this list are to advertise job vacancies, to provide students with the opportunity to contact these research groups directly to obtain information for thesis

assignments and to promote cooperation, networking and the exchange of ideas between researchers. [<http://www.invitrojobs.com/index.php/en.html>]

[UCDavis Centre for Animal Alternatives Information](#) places special emphasis on disseminating up-to-date information concerning animal alternatives through every level of public and private education. It also seeks to provide investigators who use animals with information on the most current methods for improving all aspects of animal care during their work. [<http://lib.ucdavis.edu/dept/animalalternatives/>]

Other resources

[CAMARADES](#) provides a supporting framework for groups involved in the systematic review and meta-analysis of data from animal studies in experimental studies in this section relating to Systematic Reviews [<http://www.dcn.ed.ac.uk/camarades/default.htm>]

[Consensus meetings on the care and use of fish, wildlife and agricultural animals in research](#) is provided by Norecopa. It contains presentations, guidelines and consensus statements from four international meetings covering all Three Rs, is in English and free of charge. [<http://www.norecopa.no/sider/tekst.asp?side=21>]

[Films showing handling and basic techniques in common laboratory animal species](#) Produced by Norecopa containing sort films, which alternatively can be viewed as slide series, illustrating common techniques. It is in English and free of charge. [<http://film.oslovet.norecopa.no/>]

[Global list of guidelines related to laboratory animal science](#). The website is maintained by Norecopa. It covers all Three Rs, is in English and free of charge. [<http://www.norecopa.no/sider/tekst.asp?side=23>]

[Guidelines for the care and use of animals in research and teaching](#). The website is maintained by Norecopa. It covers all Three Rs, is in English and free of charge. [<http://oslovet.norecopa.no/fag.aspx?fag=65>]

[Guidelines on the care and use of fish in research](#). The website is maintained by Norecopa. It covers all Three Rs, is in English and free of charge. [<http://oslovet.norecopa.no/dokument.aspx?dokument=148>]

[Guidelines for "Good Scientific Practice"](#) from the Deutsche Forschungsgemeinschaft (available in English). They may apply for a Three R information retrieval and the way, the retrieved information is processed and discussed in the project applications (to safeguard transparency, etc.). [http://www.dfg.de/en/research_funding/principles_dfg_funding/good_scientific_practice/index.html]

German language web-sites for "**best practice**" in **breeding, accommodation, care and use of animals**: <http://www.tierschutz-tvt.de/> ; <http://www.gv-solas.de/>

[Procedures with Care website](#) by Newcastle University, NC3Rs and IAT, provides a series of resources to support the adoption of best practice for commonly used

procedures in animal research. The focus is on rats and mice but further material will be added to expand the range of techniques and species in the future.
[<http://www.procedureswithcare.org.uk/>]

[Searching for 3Rs Information - Published Literature Sources](#): The UK Pharmaceutical Industry document assists researchers and information professionals in the pharmaceutical industry to retrieve relevant information on animal alternatives and the 3Rs. It covers core 3Rs journals 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 and selected other information resources.

[http://www.impi.org.uk/i3r_v2_jul2002.pdf]

Organisations in the field of Three Rs

[American Association for Laboratory Animal Science \(AALAS\)](#)

[<http://www.aalas.org/>]

[European consensus-platform for alternatives \(ECOPA\)](#)

[<http://www.ecopa.eu/>]

[The Federation of Laboratory Animal Science Associations \(FELASA\)](#)

[<http://www.felasa.eu/>]

[Institute of Animal Technology \(IAT\)](#)

[<http://www.iat.org.uk/>]

[International Council for Lab Animal Science \(ICLAS\)](#)

[<http://www.iclas.org/>]

[Laboratory Animal Veterinary Association \(LAVA\)](#)

[<http://www.lava.uk.net/>]

[Nationaal Kenniscentrum Alternatieven voor dierproeven \(NKCA\)](#)

[<http://www.nkca.nl/>]

[The Royal Society for the Prevention on Cruelty to Animals \(RSPCA\)](#)

[<http://www.rspca.org.uk/home/>]

[Universities Federation for Animals Welfare \(UFAW\)](#)

[<http://www.ufaw.org.uk/>]

Appendix II
ARRIVE guidelines

<http://www.nc3rs.org.uk/page.asp?id=1357>

The ARRIVE guidelines Animal Research: Reporting *In Vivo* Experiments

Carol Kilkenny¹, William J Browne², Innes C Cuthill³, Michael Emerson⁴ and Douglas G Altman⁵
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Statistics in Medicine, University of Oxford, Oxford, UK.

	ITEM	RECOMMENDATION
TITLE	1	Provide as accurate and concise a description of the content of the article as possible.
ABSTRACT	2	Provide an accurate summary of the background, research objectives, including details of the species or strain of animal used, key methods, principal findings and conclusions of the study.
INTRODUCTION		
Background	3	<ul style="list-style-type: none"> a. Include sufficient scientific background (including relevant references to previous work) to understand the motivation and context for the study, and explain the experimental approach and rationale. b. Explain how and why the animal species and model being used can address the scientific objectives and, where appropriate, the study's relevance to human biology.
Objectives	4	Clearly describe the primary and any secondary objectives of the study, or specific hypotheses being tested.
METHODS		
Ethical statement	5	Indicate the nature of the ethical review permissions, relevant licences (e.g. Animal [Scientific Procedures] Act 1986), and national or institutional guidelines for the care and use of animals, that cover the research.
Study design	6	<p>For each experiment, give brief details of the study design including:</p> <ul style="list-style-type: none"> a. The number of experimental and control groups. b. Any steps taken to minimise the effects of subjective bias when allocating animals to treatment (e.g. randomisation procedure) and when assessing results (e.g. if done, describe who was blinded and when). c. The experimental unit (e.g. a single animal, group or cage of animals). <p>A time-line diagram or flow chart can be useful to illustrate how complex study designs were carried out.</p>
Experimental procedures	7	<p>For each experiment and each experimental group, including controls, provide precise details of all procedures carried out.</p> <p>For example:</p> <ul style="list-style-type: none"> a. How (e.g. drug formulation and dose, site and route of administration, anaesthesia and analgesia used [including monitoring], surgical procedure, method of euthanasia). Provide details of any specialist equipment used, including supplier(s). b. When (e.g. time of day). c. Where (e.g. home cage, laboratory, water maze). d. Why (e.g. rationale for choice of specific anaesthetic, route of administration, drug dose used).

	ITEM	RECOMMENDATION
Experimental animals	8	<p>a. Provide details of the animals used, including species, strain, sex, developmental stage (e.g. mean or median age plus age range) and weight (e.g. mean or median weight plus weight range).</p> <p>b. Provide further relevant information such as the source of animals, international strain nomenclature, genetic modification status (e.g. knock-out or transgenic), genotype, health/immune status, drug or test naïve, previous procedures, etc.</p>
Housing and husbandry	9	<p>Provide details of:</p> <p>a. Housing (type of facility e.g. specific pathogen free [SPF]; type of cage or housing; bedding material; number of cage companions; tank shape and material etc. for fish).</p> <p>b. Husbandry conditions (e.g. breeding programme, light/dark cycle, temperature, quality of water etc for fish, type of food, access to food and water, environmental enrichment).</p> <p>c. Welfare-related assessments and interventions that were carried out prior to, during, or after the experiment.</p>
Sample size	10	<p>a. Specify the total number of animals used in each experiment, and the number of animals in each experimental group.</p> <p>b. Explain how the number of animals was arrived at. Provide details of any sample size calculation used.</p> <p>c. Indicate the number of independent replications of each experiment, if relevant.</p>
Allocating animals to experimental groups	11	<p>a. Give full details of how animals were allocated to experimental groups, including randomisation or matching if done.</p> <p>b. Describe the order in which the animals in the different experimental groups were treated and assessed.</p>
Experimental outcomes	12	Clearly define the primary and secondary experimental outcomes assessed (e.g. cell death, molecular markers, behavioural changes).
Statistical methods	13	<p>a. Provide details of the statistical methods used for each analysis.</p> <p>b. Specify the unit of analysis for each dataset (e.g. single animal, group of animals, single neuron).</p> <p>c. Describe any methods used to assess whether the data met the assumptions of the statistical approach.</p>
RESULTS		
Baseline data	14	For each experimental group, report relevant characteristics and health status of animals (e.g. weight, microbiological status, and drug or test naïve) prior to treatment or testing. (This information can often be tabulated).
Numbers analysed	15	<p>a. Report the number of animals in each group included in each analysis. Report absolute numbers (e.g. 10/20, not 50%).</p> <p>b. If any animals or data were not included in the analysis, explain why.</p>
Outcomes and estimation	16	Report the results for each analysis carried out, with a measure of precision (e.g. standard error or confidence interval).
Adverse events	17	<p>a. Give details of all important adverse events in each experimental group.</p> <p>b. Describe any modifications to the experimental protocols made to reduce adverse events.</p>
DISCUSSION		
Interpretation/scientific implications	18	<p>a. Interpret the results, taking into account the study objectives and hypotheses, current theory and other relevant studies in the literature.</p> <p>b. Comment on the study limitations including any potential sources of bias, any limitations of the animal model, and the imprecision associated with the results².</p> <p>c. Describe any implications of your experimental methods or findings for the replacement, refinement or reduction (the 3Rs) of the use of animals in research.</p>
Generalisability/translation	19	Comment on whether, and how, the findings of this study are likely to translate to other species or systems, including any relevance to human biology.
Funding	20	List all funding sources (including grant number) and the role of the funder(s) in the study.

The ARRIVE guidelines: Animal Research: Reporting In Vivo Experiments. Originally published in *PLoS Biology*, June 2010⁷



The guidelines are intended to:

- Improve reporting of research using animals
- Guide authors as to the essential information to include in a manuscript, and not be absolutely prescriptive.
- Be flexible to accommodate reporting a wide range of research areas and experimental protocols.
- Promote reproducible, transparent, accurate, comprehensive, concise, logically ordered, well written manuscripts.
- Improve the communication of the research findings to the broader scientific community.

The guidelines are NOT intended to:

- Promote uniformity, stifle creativity, or encourage authors to adhere rigidly to all items in the checklist. Some of the items may not apply to all studies, and some items can be presented as tables/figure legends or flow diagrams (e.g. the numbers of animals treated, assessed and analysed).
- Be a guide for study design and conduct. However, some items on the checklist, such as randomisation, blinding and using comparator groups, may be useful when planning experiments as their use will reduce the risk of bias and increase the robustness of the research.

What kind of research areas do the guidelines apply to?

- The guidelines will be most appropriate for comparative studies, where two or more groups of experimental animals are being compared; often one or more of the groups may be considered as a control. They apply also to studies comparing different drug doses, or, for example, where a single animal is used as its own control (within-subject experiment).
- Most of the recommendations also apply to studies that do not have a control group.
- The guidelines are suitable for any area of bioscience research where laboratory animals are used.

Who are the guidelines aimed at?

- Novice and experienced authors
- Journal editors
- Peer reviewers
- Funding bodies

How might these guidelines be used?

The guidelines provide a checklist for those preparing or reviewing a manuscript intended for publication.

References

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2. Schulz KF, Altman DG, Moher D, the CONSORT Group (2010) CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 340:c332.

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†Please note: that the working group members who contributed to these guidelines were advising in their personal capacity and their input does not necessarily represent the policy of the organisations with which they are associated.

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Appendix III

Further reading regarding literature search

- Good Search Practice on Animal Alternatives – The (ECVAM/European) Search Guide for Inexperienced Database Users
- Chilov, M., Matsoukas, K., Ispahany, N., Allen, T. Y., Lustbader, J. W., 2007, Using MeSH to search for alternatives to the use of animals in research. *Med Ref.Serv.Q*, 26(3), p. 55-74
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