

How can standardised reporting of animal research advance the 3Rs?

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艾德里安·史密斯 (Adrian Smith): 挪威 3R 原则国家共识平台 (Norecopa) 教授, 英国兽医, 出生于 1955 年。1979 年从剑桥大学获得兽医医学学位。在英国进行混合兽医执业 1 年后, 于 1980 年移居挪威。1988 年, 他凭借论文“美国蓝狐 (*Alopex lagopus*) 睾丸活动的季节性改变”获得博士学位。同年, 他被任命为毛皮动物和实验动物健康教授。1991 ~ 2009 年, 受雇于挪威兽医学院, 从事与实验动物相关的各种工作。2003 ~ 2011 年间, 艾德里安·史密斯担任欧洲实验动物医学会专家, 直到他离开兽医学院。艾德里安·史密斯与挪威主管部门紧密合作, 参与制定实验动物科学教育和培训的国家要求; 合作起草挪威现行动物实验管理规定; 参与制定兽医护理员培训课程以及开发 3R 原则国家共识平台。2005 ~ 2006 年, 他领导临时 3R 原则平台工作, 并在 2007 年平台正式成立后, 成为 Norecopa 平台永久的秘书长 (www.norecopa.no)。

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Brief introduction:

Adrian Smith is a British veterinarian, born in 1955. He obtained his degree in Veterinary Medicine at Cambridge University in 1979. After a year in mixed veterinary practice in England, he emigrated to Norway in 1980. He took his doctoral degree on the “seasonal changes in testicular activity in the blue fox (*Alopex lagopus*)” and was appointed Professor in the health of furbearing animals and laboratory animals in 1988.

From 1991 to 2009, He was employed at the Norwegian School of Veterinary Science in a range of positions, all related to the use of animals in research.

He was a Diplomate of ECLAM (European College of Laboratory Animal Medicine) from 2003 until he left the Veterinary School in 2011. He has collaborated closely with the Norwegian authorities, including development of national requirements for education and training in laboratory animal science; co-authorship of the draft of Norway's current Regulation on animal experimentation; participation in the creation of a course for the training of veterinary nurses; and the development of a national consensus – platform for the 3Rs.

He led the work of a temporary 3R – platform in 2005 – 2006 and became secretary of the permanent platform, Norecopa (www.norecopa.no), when it was established in 2007.

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【Abstract】 Although the publication of peer-reviewed scientific papers is the major way in which scientists communicate with one another, these papers often lack essential information about the conditions under which the animals lived and how they were treated during the experiments. Without this information it may be impossible to evaluate the studies, replicate them in another laboratory, or use them to advance the 3Rs in other animal experiments. This paper gives some advice on how the reporting of animal research can be improved.

【Key words】 Laboratory animal; 3Rs; Animal welfare

Introduction

Good reporting of animal research is an essential part of the quality control of the use of laboratory animals (Figure. 1). Without it, researchers planning new experiments will not be able to discover experiments which have already been performed, and therefore risk using animals unnecessarily.

Despite that fact that it is in researchers' own interests to report experiments clearly, there is plenty of evidence that this is not the case.

Jane Smith and coworkers^[1] examined 149 papers published in 8 journals from 1990 – 1991. Among the parameters not mentioned in these papers were:

- Number of animals: 30%
- Number of animals per cage: 73%
- Sex of the animals: 28%
- Age of the animals: 52%
- Weight of the animals: 71%
- Source of the animals: 53%
- Room temperature: 72%
- Relative humidity in the room: 89%
- Daylength in the animal room: 72%
- How the animals were killed: 45%

Whereas there were often detailed descriptions of the chemicals and equipment used and treatments performed, little was written about the animals themselves (where the greatest source of variability lies), including choice of sample size and whether the animals were randomised to the treatment groups or not. Many of these omissions make it more difficult to advance the 3Rs, since practical techniques such as methods of drug administration, blood sampling, anaesthesia, analgesia and humane endpoints all play important roles in defining how much suffering the animal is subjected to. Knowledge of the methods used may also be essential if the experiment is to be reproduced in another laboratory. Kilkenny and coworkers^[2] found similar results in 271 papers, mostly published in 2003 – 2005.

Bearing in mind that large bibliographic databases may only cite the title and abstract of an article, it is crucial that these are used actively to promote any advances in the 3Rs which the paper may describe. Of-

ten, however, these are rather uninformative. All researchers should be aware of the responsibility which they have to disseminate information about new 3R techniques, and should write their papers accordingly.

For example, the first paper which described the use of the saphenous vein for blood sampling in mice did not mention the technique in the title or abstract. It was not until a separate paper was written with the title *Saphenous vein puncture for blood sampling of the mouse, rat, hamster, gerbil, guinea-pig, ferret and mink* that this technique became widely known^[3]. This paper has for many years been the second or third most cited publication in the journal *Laboratory Animals*^[4].

Publication of a new 3R technique does not have to be done in a high-impact journal. The most important aspect is to make sure it is indeed published, so it can be found by search engines and cited.

Ideally, the Materials & Methods section of a paper should be so detailed that it is possible to reproduce the study in another laboratory. However, this information takes space. There are two solutions to this challenge:

1. The first is to avoid all unnecessary or meaningless words in the text in the journal, e. g. 'drinking' water, 'farm' pigs, 'standard conditions'.

2. The second solution is to publish the remaining information elsewhere. Many journals now offer supplementary online space (which is generally unlimited) where more information about the methods and results can be posted. Failing that, most research institutions have access to a website where this information can be placed and referred to in the paper.

Increasing attention is now being focused on the fact that negative results are not published as frequently as positive ones. This automatically causes an incorrect bias in the literature towards positive results. Negative results may be just as important for the scientific community, even if they are less newsworthy. To counter this, many medical journals require registration of trials before they start, to prevent the under-reporting of negative results^[5]. There are also now a number of journals dedicated to reporting negative results, such as:

- the Journal of Negative Results^[6]

- the Journal of Negative Results in Biomedicine^[7]
- the Journal of Pharmaceutical Negative Results^[8]
- The All Results Journals^[9].

Guidelines for standardised reporting

Good reporting helps researchers better plan their own experiments to identify and ensure the quality of the critical points which may fail if these are not sufficiently attended to. Identification of the most critical points in an experiment should be performed both for animal welfare reasons and to ensure the scientific value of the experiment. When these points have been identified, sufficient resources can be allocated to prevent failure.

Standardised reporting and increased implementation of the 3Rs is also dependent upon a culture of care among staff at all levels of the animal facility. Quality assurance can be achieved by putting in place a number of procedures at different levels in the system;

- Standard Operating Procedures (SOPs) which describe how to perform the techniques
- Education and training in these procedures, to ensure competence
- A checklist describing all the parameters to be reported in the scientific paper. This checklist can then be used on a daily basis by all those involved in the experiment. It can also serve as a contract between the researcher and the facility, so that nothing is forgotten and no doubt exists as to who has responsibility for measuring parameters at the various stages of the study.
- A description of the operation of the facility. The AAALAC Program Description template^[10] can be very useful for this purpose, even if AAALAC accreditation is not being applied for, because it covers all four major areas of the operation of facility:
 - Institutional policies on animal care and use
 - Animal environment, housing and management
 - Veterinary care
 - Physical plant
 - Finally, a Master Plan should be written, de-

scribing tasks which need to be performed during the year and which otherwise easily get forgotten, particularly if they are not performed often, such as service of equipment.

In addition to these checklists, there now exist several guidelines on how to report animal experiments, to ensure that essential information is not forgotten. The most well-known ones are the ARRIVE guidelines^[11], which also are available in Mandarin^[12] and which have been adopted by many scientific journals. Among other similar guidelines is the Gold Standard Publication Checklist^[13], the authors of which have published a comparison with ARRIVE^[14].

Use of the Internet to find 3R resources

With the free availability of information on the Internet, it may be tempting to assume that literature searching skills are no longer needed. The very opposite is true, if relevant papers are to be located among millions of other texts. Indeed, a quick glance at the Internet shows that papers describing 3R advances are not easy to locate.

The World Wide Web consists of two parts, that have been called *The Surface Web* and *The Deep Web*. The Surface Web, which is that part searched by the search engines, is useful for locating a specific document which the researcher knows exists, or for looking for a starting-point for information on a specific topic. Likewise, it is useful for finding so-called “grey literature”, such as reports which are not published in the scientific literature but which may be available on, for example, institutional websites. These reports may be just as valuable scientifically as published papers at some stages when planning experiments.

The Deep Web is several orders of magnitude larger than the Surface Web. The reasons why this material is less accessible include:

- The use of encryption
- Password-protected sites requiring registration or subscription
- Material which is not formatted for standard

search engines, such as text in images or video files.

It should therefore be clear that scientists need access to specialist sources of information if they are to locate the resources they need to advance the 3Rs.

Databases, guidelines, information centres, journals and discussion groups

The fact that scientists all too rarely use 3R terms in the titles, keywords or abstracts of their papers, is made worse by the fact that many are not aware of the many specialist databases, which should be searched as well as the better known and larger bibliographic databases such as MEDLINE. There is also relatively poor overlapping between these databases, so one search in a large database, even if it returns thousands of hits (many of which will prove to be irrelevant), is not sufficient. Neither do we have one “Journal of Alternatives to Animal Experiments” to search in; the advances that have been made in the 3Rs are published alongside papers on very different topics.

In addition, the growth of the Internet has resulted in an enormous number of websites containing information of relevance to the 3Rs and a large number of specialist databases. Many laboratory animal facilities have their own lists of resources, but these are often rather random, infrequently updated and not particularly comprehensive.

In 2005, Smith and Allen published a paper giving a global overview of available databases, information centres and guidelines which may be of use when planning research that may involve animals^[15]. In 2014 this information was updated and transferred to a database:

- 3R Guide^[16]: information on approx. 320 guidelines, databases, information centres, journals and discussions groups of relevance to the 3Rs (<http://www.3RGuide.info>).

The 3R Guide database supplements two other databases hosted by Norecopa:

- NORINA^[17]: information on approx. 3,600 audiovisual products which can be used as alternatives

or supplements to the use of animals in education and training (<http://oslovet.norecopa.no/NORINA>)

- TextBase^[18]: information on approx. 1,600 textbooks and other literature within Laboratory Animal Science and the 3Rs (<http://oslovet.norecopa.no/Textbase>)

All these three databases can be searched using an intelligent search engine at <http://search.norecopa.no>.

World Congresses on the 3Rs

Another important source of information on the 3Rs, and a driving force for their implementation, is the series of World Congresses on Alternatives and Animal Use in the Life Sciences which have been held every 2–3 years since 1993. The most recent of these was the 9th Congress in Prague in 2014^[19], where there were over 890 abstracts and 1000 participants from 49 countries. The next Congress is to be held in Seattle in 2017.

National 3R Centres

Many national 3R centres now exist, such as the NC3Rs in the UK^[20] and the National Consensus Platforms that are members of the European Consensus-Platform on Alternatives, *ECOPA*^[21]. Several animal welfare organisations have also scientific departments performing valuable tasks related to the 3Rs, and these should also be consulted when planning a literature search. These include UFAW^[22], FRAME^[23] and the RSPCA^[24] in the UK.

Discussion Groups

The ease in which electronic discussion groups can now be set up, using email, has led to a large number of groups of relevance to the 3Rs. These may be a useful starting point if an initial literature search is fruitless. One of the largest and oldest is CompMed (Comparative Medicine List)^[25]. More examples may be found in the 3R Guide database^[26].

Journals

Likewise, there is now a large number of journals of relevance to laboratory animal science and the 3Rs. Not all of these are well-known to scientists. Again, the 3R Guide database provides a list, sorted by

scientific discipline^[27]. Many of these have published theme numbers. The papers in these may be a good starting-point for a literature search, even if they are a few years old, because they help to identify key institutions and researchers within the field. These can then be contacted to access the latest knowledge in that area.

Guidelines

Scientific papers which refer to guidelines on the care and use of animals in research will indirectly contribute to the advancement of the 3Rs by signalling to other researchers that there are standards to follow. Many guidelines have been produced locally, for example by the institutional care and use committee, but an increasing number have been produced by specially appointed working groups and are published in peer-reviewed journals. A search should always be made, when planning an experiment, for relevant guidelines for the various stages of the study. A global collection of guidelines is available in the 3R Guide database^[28].

Consensus meetings on areas of animal use may also be useful sources of guidance for future research, since these often discuss problem areas and suggest solutions. For example, Norecopa has arranged international consensus meetings on harmonisation of the care and use of fish, wildlife and agricultural animals. All presentations from these meetings are available on the internet, where they function as a lasting resource, also for those who did not attend. At these meetings, the participants also wrote consensus statements describing the strengths, weaknesses and challenges within each area. Such documents are a good way of highlighting areas of concern so that others can take up the challenge and work to solve the issues raised. A similar set of meetings is being arranged in the UK^[29].

At the 2nd World Congress in Utrecht in 1996, an initiative was taken to form what became Altweb (Alternatives to animals on the web)^[30] in 1997. Altweb is now one of several websites offering comprehensive information on the 3Rs and a search guide. Similar search guides have been produced by others, including the Canadian Council on Animal Care (CCAC)^[31].

Guidelines for good literature searches

Good reporting is valueless if literature searches are not performed correctly. These are therefore an essential part of the work to advance the 3Rs. Many scientists need professional help to construct an adequate search and advice on which specialist databases they should use.

When performing a search, it can be equally frustrating to retrieve too few hits as it is to retrieve many thousand. A combination of search efficiency (minimising the number of irrelevant or poor-quality results) and search effectivity (maximising the number of high-quality results) must be sought after. Writing one long search string into an Internet search engine will not produce this result.

As a general principle, the following basic search strategies should be followed:

- Define the search as well as possible
- Identify synonyms and 3R terms
- Remember the differences between British and American English
- Use several databases (there is often little overlapping)
- Learn the differences between the search engines and their default settings
- Get used to using Boolean operators to expand or narrow a search, and check which terms are supported by the search engine
- Look for core articles and key authors
- Use the possibilities on the Internet to get in touch with key research labs

Knowledge of which Boolean operators (e. g. the terms AND, OR, NOT) and other commands are supported by the search engine in question is essential. Truncation of search terms using wildcards (for example ? or *) may be a good way to increase hits, but this may also lead to unwanted results. Time should be taken to read the user manual before attempting a search using any search engine.

Identifying suitable search terms may be a problem, particularly if the scientist is unfamiliar with the field or has a poor grasp of the English language. In

these cases a thesaurus or synonym list will be helpful. A thesaurus is a closed list of terms used to index and search databases. A synonym list is a collection of words with similar meanings (e. g. “heart” and “cardiac”). It is often a good idea to start a literature search with a database that uses a thesaurus. Examples of thesauri are:

- the MeSH (Medical Subject Headings) used by PubMed at the US National Library of Medicine, where “animal use alternatives” is one search term^[32]
- the US National Agricultural Library’s thesaurus for alternatives to animals^[33]
- EURL ECVAM’s thesaurus within *in vitro* toxicology^[34]

The Animal Welfare Information Center (AWIC) at the US Department of Agriculture has also made some sample searches available for guidance^[35].

In addition to these principles, the search itself should be performed in several parts, and only after this has been done should the individual parts be combined^[36]. By doing this, it is easier to refine (increase or decrease) the hits obtained for each part of the search. A typical research study involves three aspects:

- The animal model
- The intervention to be carried out on that animal model
- The disease or condition which comprises the research interest

In many studies there is also a fourth component: the disease or condition in the target species (often humans) which the animal model is trying to provide information about. This is not always mentioned in the title/abstract of relevant papers and it is therefore not always a good idea to add this component.³⁷

For example, in the following study there are four Search Components (SC):

The effect of (SC1) group-housing on (SC2) blood pressure in (SC3) rats used in (SC4) diabetes research

Separate literature searches should be performed for the components before they are combined into one search string. By doing this, the search terms and re-

sulting number of hits for each component can be evaluated and adjusted before this information is pooled in the final search (SC1 AND SC2 AND SC3 (AND SC4)). This is explained in much more detail in a paper by Leenaars et al., 2012³⁷.

Search Guides

There are a number of good guides to literature searching available. They include:

- The EURL ECVAM Search Guide^[37]
- CCAC Three Rs Search Guide^[38]
- AltWeb: A step-by-step approach to an alternatives search^[39]
- UC Davis guide to bibliographic databases for alternatives searching^[40]
- IMPI I3R working party report on Searching for 3Rs Information – Published Literature Sources^[41]

The EURL ECVAM Search Guide

The EU Joint Research Centre’s Reference Laboratory for the validation of alternative methods, EURL-ECVAM^[42], has produced an excellent Search Guide, single copies of which may be obtained free of charge from the EU Bookshop³⁶. The Guide includes

- Data sheets on
- Journals
- Databases
- Open Access resources
- Organisations
- Internet search engines
- Data Retrieval Procedures
- A Check-list for searching for information on alternative methods
- Tables comparing the features of
- Databases
- Journals
- Organisations

The Guide also contains *Seven Golden Steps to Successful Searching*:

1. Clearly define and be aware of your specific information need
2. Identify the fundamental components of your scientific approach
3. Choose the most appropriate information re-

sources

4. Compile relevant and necessary search terms
5. Start your search with a simple query in a 3Rs specific context

specific context

6. Limit search results from more extensive resources

7. Broaden the search horizon

A useful summary of how to approach the planning of an experiment which may involve animals is provided by a flow diagram from the consortium of UK animal welfare organisations Focus on Alternatives (FoA). It may be downloaded free of charge from the internet^[43], together with a worked example^[44].

Systematic reviews

Systematic Reviews are methodical and standardised literature searches, as opposed to less rigorous Narrative Reviews which are more frequently carried out by researchers and are less comprehensive, and are more likely to be influenced by the writer's knowledge or interest in an area.

The great advantage of systematic reviews over narrative reviews is that they make it possible to conduct *Synthesis of Evidence* by meta-analysis of the papers found in the literature. This is the use of statistical methods to summarize the results of independent studies. In this way, new results can be obtained from animal experiments which have already been carried out, and which would not have been obvious unless a comprehensive search and analysis of the literature had been performed. This is clearly an important way of advancing the 3Rs. Guidelines for systematic reviews are available^[45,46].

Conclusions

The importance of ensuring that scientific experiments are reported in sufficient detail and in accessible sources is often underestimated. Without good reporting it is difficult to analyse the scientific literature and plan future studies where the 3Rs are given sufficient attention. Guidelines for standardised reporting should be adopted on a greater scale. To fully advance the 3Rs, it is also equally important that scientists are given

sufficient assistance to conduct thorough searches of the literature.

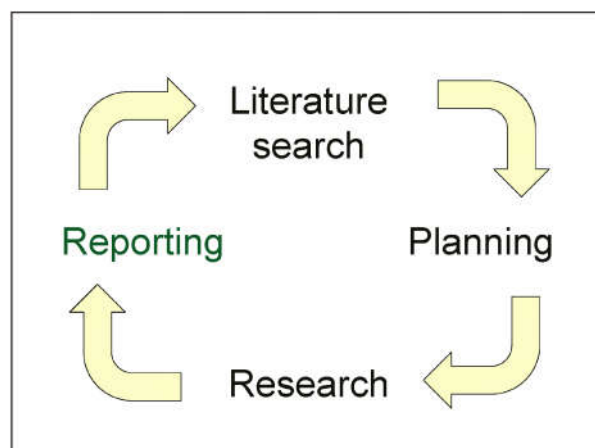
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A high standard of reporting advances the 3Rs because it facilitates the discovery of relevant literature when performing a literature search, which is an essential step when planning studies that might involve the use of animals.

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