

## EDITORIAL

# The publication in *Homeopathy* of studies involving animal experimentation



This editorial introduces a revised set of publication requirements for papers, submitted to *Homeopathy*, that involve animal experimentation. Journals that publish studies involving animal experimentation have a major role to play in the maintenance of ethical standards because researchers are reliant upon them for publication of their findings. With an increasing global trend towards greater transparency and accountability in animal experimentation, many academic journals, such as the *British Journal of Pharmacology*,<sup>1,2</sup> are taking action to improve reporting standards. In recognition of this need, members of *Homeopathy's* Editorial Board have been working together to examine the scientific rationale and the most relevant ethical guidelines for the use of animals in research. In addition, they have examined existing published studies in homeopathy research and current practice within the broad domain of medical research. Each of these aspects has informed the revised publication policy, whose overarching objectives are to maximise the ethical standards and scientific quality of animal research in homeopathy, and thereby ultimately to avoid any unnecessary suffering of animals used in such research.

The following description details the background that was considered, the rationale for this development, and the steps that will be taken.

## The animals used in research

The number of animals used in research worldwide is impossible to specify exactly because many countries do not publish relevant data. In the United Kingdom, vertebrate animals, such as mammals, fish and birds, are protected by law; the numbers of these animals used for research purposes are counted by the UK government each year. Invertebrate animals, such as fruit flies or worms, are also used in large numbers for research purposes but are neither protected by the law nor counted.<sup>3</sup> The most recently published figures available relate to the year 2013, when there were over four million (4,121,582) scientific procedures using animals in the UK.<sup>4</sup> The number of animals used will be less than this because some animals are included in, or have been subjected to, more than one procedure. The figures show that the annual number of animal procedures increased by one million (over one third) in the twelve years from 1997 to 2009.<sup>4</sup>

The use of genetically modified mice is largely responsible for recent increases.<sup>5</sup> A known and consistent genetic profile of the animals used in a study is often of advantage,

as it can reduce variability in the experiments arising from genetic variation in the animal samples studied, and can also increase the reproducibility of the results.<sup>6</sup> More importantly, through gene knockout experiments, such models can reveal the impact of given molecular pathways in the normal specimen. In 2013 alone, genetically modified mice were used in 2,511,929 scientific procedures, representing 61% of the overall total in the UK.<sup>4</sup>

Whilst we cannot determine the exact number of animals used worldwide in research, the global figure has been estimated at between 50 and 60 million animal procedures per year.<sup>3</sup> Moreover, the number of animals used in research continues to rise in many countries<sup>7</sup> and, as in the UK, the recent rises in animal procedures are mainly attributed to the increased production and use of animals with genetic modifications or defects.

Most of the animals used in research in the UK are rodents, followed by fish and birds. Taken together, dogs, cats and monkeys represent 0.2% of animals used. The following figures relate to procedures on animals in the UK in 2013:

- Rats, mice and other rodents (all purpose-bred laboratory species): 82%
- Fish, amphibians, reptiles and birds: 15.3%
- Sheep, cows, pigs and other large mammals: 2%
- Dogs, cats, non-human primates and horses (all bred for research, no strays or unwanted pets can be used): 0.4%
- Others: 0.3%.<sup>4</sup>

## The animals used in homeopathy research

Whilst it is extremely difficult to establish the exact numbers of animals that have been subjects of experimentation in homeopathy research, it is possible to gain an indication of the number of studies in question through examination of the HomBRex (Homeopathic Basic Research experiments) database.<sup>8</sup> This database details studies that fall under the category of 'basic research' in the field of homeopathy and it currently lists 2180 published experiments, of which 1638 are original articles. Our search of the HomBRex database for studies involving animals in November 2015 showed that of the published papers, 1090 mentioned use of animals. Table 1 shows the breakdown of this number by species.

In addition to scrutiny of the HomBRex database, original research articles published in *Homeopathy* over the

**Table 1** Studies involving animals retrieved from HomBRex database, Nov 2015

Animal	Number of papers retrieved
Rats	361
Mice	366
Guinea pigs	48
Hamsters	1
Fish	8
Frogs	57
Toads	13
Birds	42
Sheep	2
Cows	21
Pigs	42
Other large animals	2
Dogs	20
Cats	5
Non-human primates	9
Horses	2
Rabbits	49
Unspecified	42
<b>Total</b>	<b>1090</b>

past 10 years (2006–2015) were analysed to establish the number that involved animal experimentation (Table 2) and the breakdown of this number by species (Figure 1).

These figures show that, over this 10-year period, 18.7% of studies published in *Homeopathy* concerned animal experimentation. The vast majority of these studies involved rats, mice and other rodents (74%), as was the case for studies listed on the HomBRex database (71%) and for the entire number of procedures on animals in the UK in 2013 (82%).

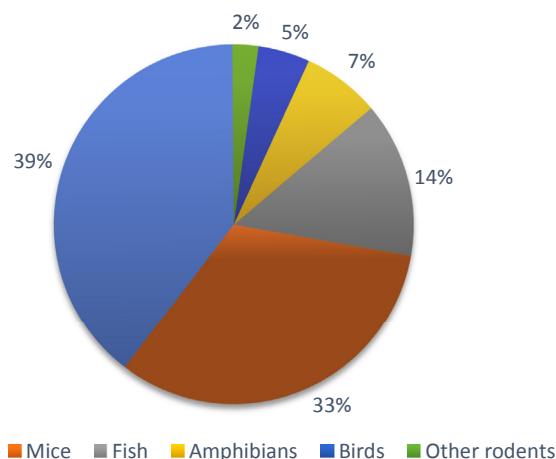
## Why animals are used in medical research

Animals are used for many different purposes in medical and pharmaceutical research. Most are used in the development and testing of medical and veterinary drugs, including vaccines.<sup>9</sup> As well as the intended benefits to humans, medicines and vaccines for companion animals and livestock also rely upon experimental animal research, and the majority of the medicines used for animals are derived from those used in humans. In addition, there are some treat-

**Table 2** Published studies involving animal experimentation\* over a 10-year time scale (*Homeopathy*, 2006–2015)

Year	Total number of original research articles	Total number of animal experimentation studies	Animal experimentation studies as % of total
2006	18	3	16.7
2007	18	0	0
2008	20	5	25
2009	20	5	25
2010	16	2	12.5
2011	15	4	26.7
2012	28	7	25
2013	26	6	23.1
2014	24	5	20.8
2015	45	6	13.3
<b>Total</b>	<b>230</b>	<b>43</b>	<b>18.7</b>

\* Excludes studies in veterinary medicine.



**Figure 1** Breakdown of published studies involving animal experimentation by species (2006–2015).

ments that are used exclusively in veterinary medicine. For example, Pasteurellosis, a severe respiratory disease, used to be common, and affected some 20% of cattle. Vaccine development involved research on about 450 calves, but it is estimated that the vaccine has prevented some 20 million cases of the disease worldwide.<sup>10</sup> The Royal Society for Prevention of Cruelty to Animals highlights the ethical dilemma this can generate:

*“The Society is opposed to all experiments causing pain, suffering or distress, yet advocates vaccination of companion animals to protect them from disease – and vaccines are currently developed and tested on animals.”<sup>9</sup>*

There are four commonly cited main reasons for using animal research:

- 1: *To advance the scientific understanding of how living creatures function.* The study of animals is viewed as a vital part of this process, as many normal biological processes, either at the cellular level or for a whole organ or physiological system, are the same in all animals or category of animals.
- 2: *As experimental models for the study of disease processes.* Humans and animals share many illnesses in common: for example, dogs are prone to cancer, diabetes, cataracts, ulcers, and bleeding disorders such as haemophilia, and rabbits often suffer from atherosclerosis, arthritis and obesity.
- 3: *In the development and testing of potential forms of treatment, especially pharmaceutical drugs.* Drugs are invariably tested on animals in preclinical studies, and data from animal studies are viewed as essential before new therapeutic drugs and procedures are tested on human patients.
- 4: *In assessment of safety.* New treatments are tested in suitable animals to reveal any potentially harmful effects.<sup>11</sup>

The categorisation of homeopathy research by these four reasons is a complex matter. It involves subjective judgment, since the author's stated aim may not fall precisely

into one or the other category. Our analysis of studies published over the past 10 years shows that most are concerned with reasons 1 and 2 (Figure 2). To date, most of these homeopathy studies have been concerned with investigating the interactions between the animal, the disease processes and the potentised remedies, with the hope that this may further an understanding of the mechanism of action of homeopathic remedies. Some of this research falls clearly into reason 1 (understanding how organisms function); some falls clearly into reason 2 (models of disease processes); and some appears to span both reasons 1 and 2.

Far fewer papers fell into reasons 3 and 4. These reasons have little relevance for homeopathy, and are difficult to justify in homeopathy research because there is no requirement for testing on animals before testing on humans (reason 3), and assessment of safety (reason 4) occurs in routine clinical practice through standard pharmacovigilance procedures.

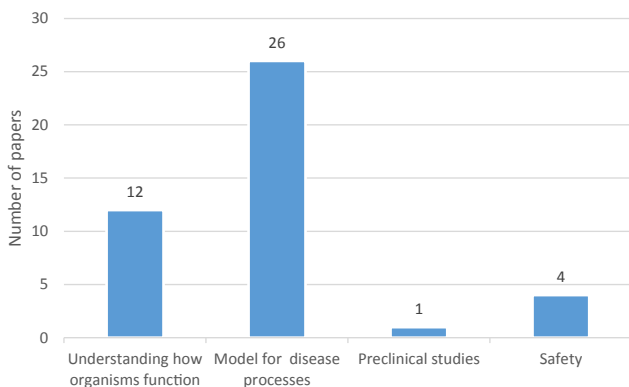
We have learned from this exercise that it is vital that researchers are clear about the precise reason for their research and that this is made explicit in publications.

## The regulation of animal use in medical research

Most existing animal research policy around the world is concerned with animal welfare and is underpinned by the notion of ‘the 3Rs’: *replacement, reduction and refinement*. It was first proposed by William Russell and Rex Burch in 1959.<sup>12</sup>

- **Replacement** refers to the idea that, wherever possible, the use of animals should be replaced with other methods that do not employ sentient creatures.
- **Reduction** concerns the decreasing of the numbers of animals needed in experiments and procedures to obtain meaningful results.
- **Refinement** refers to any factors that can decrease the incidence of severely harmful or of inhumane procedures for the animals that are used.

In the UK, the National Centre for the Replacement, Refinement and Reduction of Animals in Research (NC3Rs) leads the discovery and application of new tech-



**Figure 2** Breakdown of published studies involving animal experimentation by reason for research (*Homeopathy*, 2006–2015).

nologies and approaches to replace, reduce and refine the use of animals for scientific purposes. Central to their activities has been the development of the *ARRIVE (Animal Research: Reporting of In Vivo Experiments)* guidelines,<sup>13</sup> which have been widely adopted by academic journals to improve transparency and quality in the reporting of research involving animals.

The 3Rs also provide the foundation for European policy. On 22 September 2010, the European Union adopted Directive 2010/63/EU on the protection of animals used for scientific purposes; it took full effect on 1 January 2013. The Directive stipulates measures that must be taken to replace, reduce and refine the use of animals in scientific research. Amongst other requirements, it lays down minimum standards for housing and care, and regulates the use of animals through systematic project evaluation that requires the assessment of pain, suffering, distress and lasting harm caused to the animals.<sup>10</sup>

Ethical guidelines and regulations for the use of animals in medical research vary widely between countries. For example, in many parts of Asia there are few or no guiding principles or regulations, and levels of accountability, transparency and responsibility can be poor.<sup>14</sup> However, there are signs that in other parts of the world, such as South America, great efforts are being made to improve standards.

There are currently no overarching global standards to guide practice but, in recent years, there have been attempts from different organisations to develop global frameworks. In 2012, the International Council for Laboratory Animal Science (ICLAS) and the Council for International Organizations of Medical Sciences (CIOMS) updated their *International Guiding Principles for Biomedical Research Involving Animals*.<sup>15</sup> These principles also incorporate the 3Rs and are intended to serve as a framework of responsibility for all countries, including those with emerging research programmes.

At the same time, the Basel Declaration Society, an organisation based in Europe, is calling for all countries to sign up to their Declaration and to adopt one set of universally agreed principles. The aim of the Basel Declaration is to bring together the global community of scientists to ensure the application of ethical principles whenever animals are being used, and to call for more trust, transparency and communication on the topic of the use of animals in research.<sup>1</sup> So far, the Declaration has been accepted in many European countries and it is hoped that it will eventually be accepted by the rest of the world in the same way as the Declaration of Helsinki has been accepted internationally for research ethics standards in humans.<sup>16</sup>

## The ethical implications of animal research

Consideration of exactly how the interests of animals should be represented, awarded value, and weighed against the competing interests of humans is a vast topic of debate. Hence, the following brief synopsis can only skim the

surface of the ethical implications of animal research. It is intended, nonetheless, to help explain the development of thinking in animal ethics and the implications for animal research in homeopathy.

The idea that animals should be awarded moral consideration was greatly advanced in utilitarian ethics; as the founder of modern utilitarianism, Jeremy Bentham, famously quoted: “The question is not, Can they *reason*? nor, Can they *talk*? but, Can they *suffer*?”<sup>17</sup>

Bentham was not against the use of animals for food or for experimentation, but he expounded the view that suffering should be avoided and that animals should only be used if there was a realistic potential for good (of humanity). In other words, the potential for good to humans would need to outweigh the potential for harm to animals. Sensitivity towards the suffering of animals was also advanced, in 1838, by the challenging conclusions of Charles Darwin: “*Man in his arrogance thinks himself a great work worthy the interposition of a deity. More humble, and I believe truer, to consider him created from animals*”.<sup>18</sup> Darwin was resolute in his opinion that many animals, just like humans, are sentient beings:

*“The lower animals, like man, manifestly feel pleasure and pain, happiness and misery. Happiness is never better exhibited than by young animals, such as puppies, kittens, lambs, &c., when playing together, like our own children”*.<sup>19</sup>

In more recent years the most influential book about animal ethics, and dominating discussions in this area, has been *Animal Liberation* by Peter Singer.<sup>20</sup> Singer, like Bentham, argues for utilitarian-based animal ethics but his notion is grounded in the ‘equal consideration of interests’, which requires us to give equal weight to similar interests, regardless of species. Preference for the interests of one species over another constitutes ‘speciesism’, a prejudice that is held no more justifiable than sexism or racism. A key point in Singer's argument is that equal consideration of interests is necessary for *sentient* beings that are capable of feeling pain and suffering.

According to Singer, we must take care when we compare the interests of different species. In some situations, a member of one species will suffer more than a member of another species. In this case we should still apply the principle of equal consideration of interests, but here we must give priority to relieving the greater suffering.<sup>21</sup> Singer's line of reasoning suggests that it may be acceptable to use some animals in research if the suffering of the used animal(s) is less than the suffering that would be relieved as a result of the research. In utilitarian ethics, actions are judged by their consequences and hence, if an experiment on a small number of animals can cure a disease that affects hundreds, it could be justifiable. Singer believes that animal studies may, in certain circumstances, be justifiable but the interests of animals count equally amongst the consequences to be considered. In practice, however, animals are not able to represent their own interests. Therefore, it is the job, prospectively, of the reviewers on the ethics committees that govern animal

research or, retrospectively, of the reviewers of *Homeopathy* for example, to consider their interests on their behalf.

The principal message from Singer's reasoning is that the ethically justifiable action is that which reduces suffering (of humans and animals) the most. We may be justified in using animals in research if the overall burden of suffering is reduced.

Additionally, where animals are used in research it is vital that their suffering is minimised. This is reflected in Directive 2010/63/EU, with specific requirements for the care and treatment of the animals. Moreover, procedures that result in severe pain, suffering or distress, which is likely to be long-lasting and cannot be ameliorated, is prohibited altogether.

## The Journal's revised policy

The aim of the revised policy is to restrict the publication of experimental animal studies in *Homeopathy* only to those that have been undertaken and reported in accordance with the foremost ethical and scientific standards, as articulated in the following account.

## Underpinning principles

In the absence of globally agreed regulation or standards for research involving animals, the underpinning principles of this policy are drawn from the Directive 2010/63/EU of the European Parliament on the protection of animals used for scientific purposes.

This directive is founded upon the principles of the ‘3Rs’ (replacement, reduction, refinement) and has the ultimate goal of full replacement of procedures on live animals for scientific and educational purposes as soon as it is scientifically possible to do so. As specified in Recital (38) of the EU Directive:

*“Comprehensive project evaluation, taking into account ethical considerations in the use of animals, forms the core of project authorisation and should ensure the implementation of principles of replacement, reduction and refinement in those projects.”*

In addition, the potential for benefit of the study (to humans, animals or the environment) must outweigh the potential for harm to the animals, as declared in Recital (39):

*“It is also essential, both on moral and scientific grounds, to ensure that each use of an animal is carefully evaluated as to the scientific or educational validity, usefulness and relevance of the expected result of that use. The likely harm to the animal should be balanced against the expected benefits of the project.”*

Academic journals have a crucial role to play in setting and maintaining ethical and scientific standards because they are the primary vehicles for the dissemination of findings. If researchers wish to publish the results of their work, they must meet the standards required by journals.

The regulation of animal research and standards of animal welfare varies widely between regions of the world.



Certain types of animal research that would be deemed unethical and unlawful within the EU are conducted in places where regulation is not as stringent. The exportation of unethical research practices to areas where regulation is less well developed is termed 'ethics dumping' and, in the case of animals, may effectively result in the 'export' of animal cruelty.

Journals can help to prevent the practice of ethics dumping by applying the same ethical standards to papers that are received from anywhere in the world. In this way they can help to facilitate the development of high ethical standards globally.

The full adoption of Directive 2010/63/EU as the required standard for all research submissions involving animal experimentation implies that non-compliance will preclude publication in the journal.

## The next steps

Researchers who are considering submitting research articles to *Homeopathy* will find an upgraded *Guide for Authors*<sup>22</sup> that continues to be based upon compliance with Directive 2010/63/EU. From 1 January 2017, authors must include in their manuscript: a check-list that illustrates compliance with each of the 20 items in the *ARRIVE* guidelines; explicit compliance with the 3Rs; an analysis of the benefit/harm ratio; a description of the relevant ethical approval.

Readers will be able to see this change in action since, while reflecting full compliance with the *ARRIVE* guidelines, authors must include the following information in the Methods section of their manuscript:

- A detailed description of how each of the 3Rs has been addressed.
- Detailed justification for the use of animals in their research through analysis of the potential benefits and harms of the study. Here they must describe how the benefits potentially derived from the research are significant in relation to any harm endured by the animals.
- A statement describing the ethical approval for experimentation, including the nature of the ethical review process and how the research complies with EU Directive 2010/63/EU.<sup>a</sup>

Extra space has been accommodated in the journal to enable comprehensive description of these issues concerning animal welfare.

<sup>a</sup>For practice-based research in *veterinary medicine on client-owned animals*, the ethical approval required must be that of a national standard-setting veterinary authority (e.g. the Royal College of Veterinary Surgeons [RCVS] in the United Kingdom). As per RCVS guidelines, "A pragmatic threshold for the need for formal ethical review is any study where a reasonable person would expect to obtain permission from the owners or keepers of an animal before including that animal in that study." (<http://www.rcvs.org.uk/document-library/rcvs-bva-ethical-review-working-report-2013/>).

Henceforth, submitted papers that report the use of experimental animals will be subjected to standard scientific review *as well as to specific ethical review*; the standard scientific review process will not preclude the consideration also of animal research ethics. Submitted papers detailing animal experimentation will be reviewed by a specialist designated member of the journal's Editorial Board, and clarification about matters of experimental research ethics will be sought from the original authors when required. Peer-reviewer guidelines, which will be formally implemented from 1 January 2017, have been developed to aide consistency in this process. Papers that do not comply with the required ethics standards will be rejected, and without the option for re-submission of the same research report.

Lastly, the Editor and the Senior Deputy Editor take responsibility for ensuring that, where relevant to homeopathy research, changes to EU legislation on the protection of animals used for scientific purposes, and/or any global initiatives on the same, are reflected in suitable updates to the journal's policy.

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