Understanding ANIMAL RESEARCH

January 2012

Animal testing and the Safety of Medicines Bill 2010

Millions of people owe their lives to medical advances. But despite continuing research there are still diseases without adequate treatments – for example dementia, many cancers and heart failure. At the same time, it is essential for all doctors, patients, regulators and the bioscience sector globally that new treatments are safe and effective. Sound and sophisticated science is used at all stages of research into health and disease, and in the development of new treatments.

Animals are crucial in biomedical research, development and testing. No scientist would want to use animals where there is a viable alternative, and it would be illegal. In fact, animal studies are always a last resort and form a relatively small proportion of biomedical research and testing as a whole.

Five independent reviews[1] in the last decade have agreed that animal research and testing is essential.

Adverse drug reactions

It is a myth that adverse drug reactions are somehow caused by reliance on animal-based safety tests. In fact, new medicines are tested on far more people than animals. The majority of serious side-effects are predictable and avoidable; this is true for 93% of people admitted to hospital with a adverse drug reaction[2]. When medicines are taken according to prescribing information and the prescribers know about other medicines being taken by the patient, many serious problems can be avoided.

Rare adverse effects (occurring in less than 1 in 1000 patients) may not be detected until a medicine has been used for some time. This is because the medicine will have had to be prescribed for at least a thousand people before a single incident of a rare adverse effect occurs. It is quite possible that rare adverse effects will not be detected during either animal studies or clinical studies in humans prior to licensing.

The Safety of Medicines Bill

The Safety of Medicines Private Member's Bill is heavily backed by a pressure group called the Safer Medicines Campaign. The Bill's sponsor argues that "animal tests have let us down badly in their role of protecting us against dangerous drugs". The related EDM 475 was signed by 150 MPs. The Bill is not supported by many scientists or doctors or by government.

The Bill proposes *"establishment of a Medicines Safety Evaluation Panel to compare the effectiveness of human biology-based tests and animal-based tests in assessing the safety of medicines. The panel would be required to report within two years and would have full access to all relevant records"* held by the MHRA.

We believe that the benefits of any such review would be limited and it would represent a waste of valuable resources.

Safety testing using animals

The need for new medicines to be safe and effective is well-recognised, and is a key concern for regulators and for the bioscience sector both in the UK and across the world. In fact, the vast majority of new medicines that reach the market do indeed prove to be reasonably safe after animal and non-animal tests and human trials. All these methods are used alongside each other to get the best information possible on safety. Of course, no medicine can be guaranteed to be free of side effects, and most side effects which do occur are due to the primary activity of the medicine (for example anti-coagulants might cause bleeding), to interactions with other medicines, or to improper use.

Animal methods are the only ethical way to test the effects of a potential new medicine at normal or high doses in a living animal for the first time.

Public and medical opinion

Polls[3] show that three quarters of people agree that animal research is necessary for our understanding of the body in health and disease and in the development of new medicines, as well as in safety testing. In a survey of GPs in 2006[4], 93% agreed "animal experiments have made an important contribution to many advances in medicine", and 88% agreed that "safety tests should be carried out on animals before human trials of new medicines are conducted".

1. House of Lords Select Committee on Animals in Scientific Procedures Report 2002; Animal Procedures Committee, *Review of Cost-Benefit Assessment in the Use of Animals in Research*, 2003; Nuffield Council on Bioethics *The Ethics of Research involving Animals*, 2005; Weatherall, *The use of non-human primates in research*, 2006; Bateson, *Review of Research Using Non-Human Primates*, 2011.
2. Pirmohamed M, James S, Meakin S, *et al* (2004). Adverse drug reactions as cause of admission to hospital: prospective analysis of 18,820 patients. *BMJ* 2004; 329, 5–19.
3. See for instance *Public attitudes towards animal experimentation: 2010 report*, Ipsos MORI, March 2011.
4. GP Net, J503774 Online quota-based GP omnibus service, September 2006.

Published by Understanding Animal Research, Charles Darwin House, 12 Roger Street, WC1N 2JU
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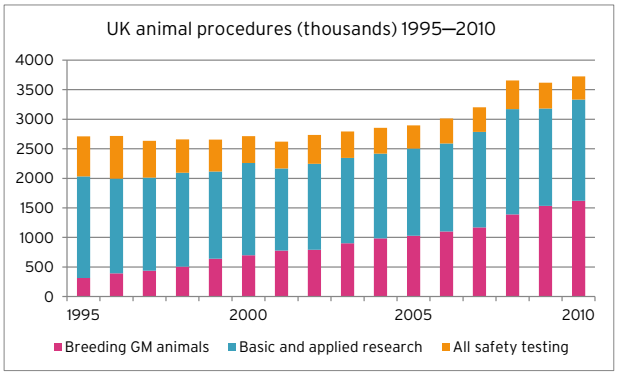
Principle 12 of the World Medical Association Helsinki Declaration, 2008, states: *"Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected."*

Regulating the use of animals in science

The use of animals in science is regulated in the UK by the Animals (Scientific Procedures) Act 1986 and in Europe by a new Directive 2010/63/EU (due to be implemented in 2013). The central principle of these very strict and detailed regulations is a cost benefit analysis, meaning that any use of animals must be justified by weighing the potential benefits against the potential welfare costs to the animals.



The major uses of animals in science are for basic and applied research, and breeding GM animals. Currently less than one tenth of animals used under the 1986 Act are used to test the safety and efficacy of medicines. This proportion has reduced since 1995 (see chart) because of efforts to minimise animal use in safety testing.

Which regulations mandate the use of animals in safety testing?

The main tests for potential medicines gauge their acute, sub-acute, and chronic toxicity (see right for explanation). European Directive 2001/83/EC, on the Community code relating to medicinal products for human use, demands that these toxicity tests are carried out in two or more mammalian species, normally one rodent and one non-rodent species.

Despite what some commentators believe, the Medicines Act 1968 does not mandate animal safety tests. The Medicines and Healthcare products Regulatory Agency (MHRA) says:

"The Medicines Act brought most previous legislation on medicines together and also introduced a number of other legal provisions for the control of medicines. It was an enabling Act providing for a system of licensing affecting manufacture, sale, supply and importation of medicinal products into the UK. It became unlawful to engage in these activities except in accordance with appropriate licences, certificates or exemptions."

Alternatives: European & OECD regulatory guidelines

These guidelines detail the regulatory toxicology tests that must be carried out before a medicine can be tested on humans. The guidelines change as science and technology evolves. Any non-animal replacement method developed must go through a process of validation before it is incorporated into regulatory guidelines.

Non-animal (or reduced animal) test methods with relevance for some specific toxicologies have now been granted regulatory acceptance by the Organisation for Economic Co-operation and Development (OECD). These relate largely to the safety testing of non-medical products, and include genotoxicity, skin irritation, skin sensitisation and aquatic toxicity.

Minimising animal use

The methods used in safety testing of medicines are subject to considerable scrutiny, and the roles of both animals and alternatives are independently investigated and endorsed. Bodies such as the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) have, for the last 20 years, developed and promoted internationally many guidelines for the safety, efficacy and quality of medicines which have minimised animal use.

Release of medicines

Safety regulators (usually MHRA or the European Medicines Agency) decide, based on all the detailed information from animal, human and other tests, whether medicines can be licensed to be released onto the market. All medicines that are marketed must comply as a minimum with the pharmacopoeia for the appropriate territory and with the specifications given in the marketing authorisation for the particular product. After licensing, medicines continue to be monitored.

↘ Acute toxicity is studied by using a rising dose until signs of toxicity become apparent.
↘ In sub-acute toxicity, a compound is given to the animals for four to six weeks in doses below the level at which it causes acute toxicity. Post-mortem studies show if any toxic metabolites have built up over time.
↘ Testing for chronic toxicity is longer term: it can last up to two years.

Conclusion

Where problems of adverse effects from medicines do occur, it is important to remember that all new medicines are tested in many more humans than animals. If a "failure" to detect a side-effect is established, all parts of the medicines testing process need to be examined, both preclinical and clinical.

The need for animals in biomedical research and testing is explained in the booklet *Where Do Medicines Come From?* published by Understanding Animal Research and supported by the Wellcome Trust.

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