Ending the Use of Animals in Toxicity Testing and Risk Evaluation

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Abstract: This article discusses the use of animals for the safety testing of chemicals, including pharmaceuticals, household products, pesticides, and industrial chemicals. It reviews changes in safety testing technology and what those changes mean from the perspective of industrial innovation, public policy and public health, economics, and ethics. It concludes that the continuing use of animals for chemical safety testing should end within the decade as cheaper, quicker, and more predictive technologies are developed and applied.

Keywords: use of animals in testing pharmaceuticals; use of animals in testing household products; use of animals in testing pesticides; use of animals in testing industrial chemicals

Introduction

The systematic and widespread use of animals for toxicity testing and risk assessment is a relatively recent phenomenon. The first such toxicity testing conducted on behalf of public authorities in the United States, in the first decade of the twentieth century, used not animals but human volunteers. Dr. Harvey Wiley's famed Poison Squad consisted of twelve young males who were the subjects of feeding experiments from 1902 to 1904 that involved benzoate, borax, and formaldehyde.[1] The use of humans then gave way to an increasingly heavy use of laboratory animals for both safety tests and risk evaluation as well as for biomedical research. But there are many signs that safety testing approaches are now changing, and changing rapidly. That is why this article is entitled "Ending the Use of Animals in Toxicity testing and Risk Evaluation."

In 1976, when I first started promoting the concept of alternatives to the use of animals in biomedical research and safety testing, I never dreamed that I would be able to employ such a title during my advocacy career. However, I am now confident that such a goal is achievable within ten to fifteen years. In addition, I am confident that the new nonanimal paradigm will provide better human and environmental risk assessment more quickly and cheaply than the standard method of feeding chemicals to rodents (and a few nonrodents). In this article I outline the policy initiatives and technical developments that have led to this point and that support my central contention that the goal is attainable, desirable, and ethically obligatory.

Historical Background

In the 1950s, Sir Peter Medawar, a British immunologist who was awarded a Nobel Prize in 1960 for his work on transplantation immunology, suggested to Major C. W. Hume, the founder of the Universities Federation for Animal Welfare (UFAW)

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in London, that biomedical laboratory technology had advanced to the point that opportunities existed to reduce the cost to laboratory animals by modifying techniques. Encouraged by Medawar, Hume persuaded UFAW to support a project to examine the potential for humane experimental techniques,[2] resulting in *The Principles of Humane Experimental Technique*, the classic 1959 volume by William Russell and Rex Burch that would become the near-universal foundation for subsequent exploration and promotion of nonanimal alternatives.[3] In 1969, Medawar presented what was then a rather unusual argument for a biomedical scientist in a speech that was later printed in his 1972 book, *The Hope of Progress*.[4] The speech included this passage:

> The use of animals in laboratories to enlarge our understanding of nature is part of a far wider exploratory process, and one cannot assay its value in isolation—as if it were an activity which, if prohibited, would deprive us only of the material benefits that grow directly out of its own use. Any such prohibition of learning or confinement of the understanding would have widespread and damaging consequences; *but this does not imply that we are for evermore, and in increasing numbers, to enlist animals in the scientific service of man. I think that the use of experimental animals on the present scale is a temporary episode in biological and medical history, and that its peak will be reached in ten years—or perhaps sooner. In the meantime, we must grapple with the paradox that nothing but research on animals will provide us with the knowledge that will make it possible for us, one day, to dispense with the use of them altogether*.[5]

Medawar's prediction that animal use would peak within 10 years and then start to decline was remarkably prescient. According to the statistics on laboratory animal procedures collected and reported annually by the Home Office,[6] the actual peak of laboratory animal use in Great Britain occurred in 1975–76. The numbers then declined by 60–65 percent over the next 20 years, to around 2 million animal procedures in 1995, but, since then, have been climbing again and now stand at around 4 million animal procedures. The recent increase is mainly due to an explosion in the number of genetically modified mice being bred in and kept by research institutions. However, the actual use of animals in laboratory studies, as opposed to their use for breeding purposes, plateaued around ten years ago at approximately 2.2 million animal procedures and has risen only marginally since then to about 2.7 million animal procedures. The use of animals for toxicity testing and for studies of the absorption and metabolic fate of drugs and chemicals has continued to fall during this period, from around 650,000 procedures in 1995 to 375,000 procedures in 2013, a 42 percent decline. In considering these statistics, I assume that a procedure is approximately equal to one animal used.

Medawar's comment in his 1969 speech is as good a foundation for someone who is focused on reducing animal pain, distress, and suffering and, more generally, animal use in laboratories as any in the published literature. It also has the advantage of coming from a major figure in biomedical research who wrote clearly and with great insight on the process of scientific discovery.

Following the publication of the Russell and Burch volume in 1959,[7] little attention was paid the book or its thesis for the next decade. However, advocacy of alternatives to animal use—conceptualized as the three Rs: replacement, reduction, and refinement of animal use—began to pick up toward the end of the 1960s.

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By the end of the 1970s, advocacy of alternatives was gaining energy among animal advocacy organizations, and, after the Draize eye test and LD50 (lethal dose 50%) campaigns of the early 1980s, corporations involved in producing cosmetics and household products began to search for and use safety tests that did not involve live animals, such as the neutral red cell culture assay and the bovine corneal opacity and permeability assay.[8]

In other words, from the time that animal use in all laboratories peaked in the mid-1970s to the end of the twentieth century, interest in nonanimal approaches in research, especially in toxicity testing and risk assessment, grew substantially. But, despite changes in both technology and public attitudes, the rhetoric surrounding animal testing and its need has not changed significantly. Regulatory agencies and biomedical research advocates (with a few noteworthy exceptions) around the world have continued to overvalue the importance of animal testing in public safety assessment and to undervalue the potential of the new technology.

Corporate Support for Nonanimal Alternatives

Around 1975, animal advocates launched campaigns against the testing of cosmetics and toiletries on animals in both Europe and the United States. These campaigns reached peak intensity in the United States in 1980, leading to the first corporate funding explicitly for research into alternatives to animals in such testing. By the end of the 1980s, corporations in Europe and the United States were spending millions of dollars a year on research into alternatives.[9] Based on publically available figures, the three multinationals—Procter and Gamble, Unilever, and L'Oréal—have together probably devoted more than $1 billion to the development of nonanimal tests since 1980.

Although most of the campaigning has focused heavily on the use of animals to test cosmetics and toiletries, reliance on animal research and testing within the pharmaceutical industry has also been on the decline for decades, despite regular assertions from some research advocates of the critical importance of laboratory animal use.

Pharmaceutical R and D relied very heavily on animal studies during the early days of drug discovery in the 1930s and 1940s (for example, in the discovery of the sulfa drugs to treat microbial infections and the discovery of penicillin) and again after World War II. By the mid-1970s, when laboratory animal use in Great Britain peaked, the pharmaceutical industry in England was carrying out around 4 million animal procedures a year. However, by 1995, according to statistics from the U.K. Home Office, the number of animal procedures carried out for pharmaceutical development and testing had fallen to around 1 million. Over the next 17 years, this number fell even further, to around 500,000 per annum.[10] At the same time, an analysis of data on pharmaceutical R and D in Great Britain from the Association of British Pharmaceutical Industries reveals that the British pharmaceutical industry increased its R and D expenditures from around £700 million to £5,000 million (in 2012 pounds) from 1995 to 2012.[11]

If animal research and testing had continued to be employed at the same rate by the pharmaceutical industry, one would have expected the number of animal procedures to have increased (perhaps by sevenfold matching the increase in R and D expenditure from £700 million to £5,000 million) from 1995 to 2012. Yet, as R and D increased, laboratory animal use halved. It is, therefore, very apparent that

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pharmaceutical research and development is much less reliant on laboratory animals today than it was in 1975 or even in 1995, and this change is happening rather quickly. We do not have similar longitudinal data on animal use for other countries with large pharmaceutical industries, but there are snapshots indicating similar trends in the United States and in continental Europe.

Defenders of animal research might argue that the remaining use of animals by corporations (around 10% of the numbers used in the mid-1970s) will be harder to replace with nonanimal techniques, but there are suggestions from such establishment figures as Dr. Francis Collins, the director of the National Institutes of Health (NIH), that it might well be possible to abandon the heavy reliance on animal studies seen in the 1950s and 1960s. Consider the following extract from a 2011 paper by Dr. Collins in which he is discussing drug discovery and development: "With earlier and more rigorous target validation in human tissues, it may be justifiable to skip the animal model assessment of efficacy altogether."[12]

Therefore, depending on the setting in which the question of our reliance on animal research is raised, research administrators and advocates are both defending the need for animal research and beginning to hint at a new approach that need not rely on animal studies at all. There have always been a few scientists voicing arguments that animal studies are not needed or will not be needed in the relatively near future. Now we are seeing a significant increase in comments from scientists presaging a day when animals will not be needed.

Political and Policy Initiatives Supporting Nonanimal Testing

In the 1990s, the European Union, pressed by animal advocates, began to move toward a policy change that would forbid not merely the testing of cosmetic products and ingredients on animals but also the marketing of cosmetic products in which the ingredients had been tested on animals. This policy was finally implemented in 2013.[13] Today, the European Union, Israel, the State of São Paulo in Brazil, and India (representing markets encompassing 1.7 billion people) all prohibit the marketing of cosmetics and cosmetic ingredients tested on animals. In terms of the ethics of animal testing, very few people today dispute the thesis that it would be unethical to subject animals to the safety testing of chemicals that are to be used in human commerce if there are adequate alternatives.

In November 2005, then European Commission vice president Günter Verheugen and then science and research commissioner Janez Potočnik launched the European Platform for Alternatives to Animals (EPAA) to support and track progress toward the ending of laboratory animal use.[14] The EPAA provides an explicitly political platform to promote alternatives to animal tests. Its mission is supported by a majority of European voters, more than three-quarters of whom consistently indicate in public opinion polls that they oppose animal testing of cosmetics. This public opposition is mirrored elsewhere in the world. A large majority of Canadian, American, and Australian citizens oppose cosmetic testing on animals, as do the citizens of countries such as Taiwan, South Korea, and Brazil, which are not usually thought of as places where animal activism has much traction.[15]

There are currently two international consortia—Be Cruelty-Free, organized by Humane Society International, and Cruelty Free International, organized by the British Union for the Abolition of Vivisection—that are focused on ending cosmetic testing on animals. Following the successes in the EU and India, there are

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now active campaigns to have similar legislative prohibitions passed in the United States, Canada, Japan, Russia, the whole of Brazil, Australia, South Korea, and a number of smaller economies.[16] The large multinational companies that market cosmetics and toiletries are still resisting these new political initiatives, but it is only a matter of time before several more countries ban cosmetics testing on animals. Be Cruelty-Free is committed to ending all animal use in safety testing, so the cosmetics campaign is simply one step toward that larger goal.

Scientific and Regulatory Dissatisfaction with Animal Testing

Whereas members of the general public might be expected to oppose animal testing of cosmetics, there has also been a growing dissatisfaction with the predictive power of animal tests for human risk assessment among scientists and regulators. In 2004, a report by the U.S. Food and Drug Administration noted that 92 percent of new drug entities were failing during human clinical trials either because the new drugs were not effective in humans (having shown promise in animals) or because they were associated with unexpected toxicity (having been demonstrated to be safe in animals).[17,18]

A few years later, in 2007, an expert panel of the National Research Council (NRC), convened at the request of the U.S. Environmental Protection Agency (EPA), issued a report determining what toxicology testing should look like in the twenty-first century. In essence, the report concluded that the future of toxicology would be mainly nonanimal testing.[19] The June 12, 2007, press release from the National Academy of Sciences announcing the release of a new report, "Toxicity Testing in the 21st Century: A Vision and a Strategy," included the following observation: "The new approach would generate more relevant data to evaluate risks people face, expand the number of chemicals that could be scrutinized, and reduce the time, money, and animals involved in testing."

This report was presented and discussed at the 2007 annual Toxicology Forum meeting in Aspen, Colorado. Most of the participants at that meeting reportedly regarded the vision as a pipe dream. However, in 2008, the U.S. National Institutes of Health, the U.S. National Toxicology Program, and the U.S. Environmental Protection Agency signed a memorandum of understanding to pursue the goals laid out in the document.[20] The mood and attitude within U.S. toxicology circles has changed dramatically in the years since that 2007 meeting in Aspen, as evidenced by the increasing attention given to the idea of a new toxicology paradigm by the Society of Toxicology. For example, when the Society of Toxicology held the second of its "Future Tox" series of symposia early in 2014,[21] the attendees focused almost entirely on how one might achieve a new, nonanimal toxicology rather than whether the goal was realistic or when it might be achieved.

Although the toxicological literature is now replete with peer-reviewed papers that raise doubts about the usefulness of animal test data for human risk assessment, there are many indications that animal testing still retains a powerful hold. Inertia, especially as found in regulatory agencies, requires considerable effort to overcome. General acceptance that animal data is somehow preferable to nonanimal data is exemplified by the following two publications.

In 2000, an expert panel of toxicologists[22] reported that the predictive power (of human toxicity) of animal test data ranged from 43 percent for rodent studies to 63 percent for nonrodent studies and to 71 percent when both rodent and

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nonrodent results were combined. Therefore, the best outcomes for the animal testing paradigm were 71 percent when a range of species was used in the toxicity studies; but, for the most part, toxicological studies are conducted with rats and with one nonrodent species—typically a rabbit, dog, or primate. Therefore, in practice, one might expect routine animal testing to predict human toxicity somewhere between 50–60 percent of the time.

Toxicologists have often cited this study as evidence that animal studies are valuable in predicting human toxicity. For example, Friedhelm Vogel of the European Federation of Pharmaceutical Industries and Associations drew attention to this report:

> Although the use of animals forms a major part of much scientific and medical research, success seen in animal studies has not always translated to the clinic. Many potential drugs fail due to a lack of efficacy in humans or concerns about their safety. The likelihood of approval, as assessed after clinical phase 1 development, has declined over the past years[23] and needs to be improved by designing more predictive—*in vivo*—screening methods, including identification and application of appropriate biomarkers. Results from another survey[24] support the value of using two species for *in vivo* toxicology studies to predict human toxicity, as the predictive value is significantly higher in combination.[25]

A little more than a decade later, a team at the Hamner Institute in North Carolina reviewed how well the EPA's ToxCast program[26]—which employs high-throughput test methods and nonanimal approaches highlighted by the NRC report[27] to set priorities for the further testing of chemicals regulated by the EPA—was performing. The authors at the Hamner Institute reported that the EPA ToxCast program predicted outcomes accurately a little more than 50 percent of the time.[28] Despite the fact that the EPA ToxCast program had roughly the same predictive outcome as the animal studies reviewed by Olson and his colleagues a decade earlier,[29] the authors of the Hamner review concluded that the EPA program predicted actual human toxicity relatively poorly.

The conclusion one would draw from the preceding two citations is that a 50–60 percent predictive capacity (little better than a coin toss) is acceptable (and even good) when obtained in animal studies but is unacceptable when produced from in vitro systems. The predictive "success" of the animal studies comes after more than 80 years of "improvement" of animal test methods, which has attempted to increase the ability of such tests to predict human outcomes. The EPA ToxCast program has only been in action for little more than a decade. It is highly likely that there is considerable potential to improve the ability of ToxCast or similar approaches to predict human hazard and potential risk.

Economic and Time Factors

Although relevance—that is, prediction of toxicity and/or effectiveness in humans—is a very important outcome in the toxicology laboratory, there are other important factors that also need to be considered in deciding whether one should continue to focus on animal studies or switch the emphasis to a new approach, such as chemical hazard identification and risk assessment, as proposed in the 2007 NRC report.[30]

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Animal toxicity studies that aim to identify the major risks to humans from a chemical in the environment take a long time to perform (three to five years per chemical) and are expensive (several million dollars per chemical). The global laboratory capacity to conduct such studies is also relatively limited. In more than 40 years, for example, only around 600 chemicals have been subjected to the standard carcinogen bioassay in mice and rats (no nonrodent species is required). That pace of testing works out to an average of just 15 chemicals tested per year. In addition, the results have led to clear regulatory decisions in only about one-fifth of the carcinogenicity studies. There are 30,000 chemicals in the REACH files in Finland that would, in an ideal world, need to be tested for carcinogenic potential as well as a range of other toxicity endpoints.

The new approach to chemical testing being proposed would lead to a huge increase in the pace of chemical testing and would also greatly reduce the expense. The ToxCast approach has made significant use of robot-powered, high-throughput testing systems (termed "high-throughput" because they are so much faster than animal studies).[31] These systems are currently capable of testing 1,408 chemicals at 15 different concentrations in 200 different nonanimal test systems in a period of just two weeks. In other words, it is theoretically possible to test all the REACH chemicals in just one year using just one of these robot systems (the National Chemical Genomics Center [NCGC] at the NIH currently has three of these robot-powered testing systems installed and functioning). These high-throughput robot testing systems generate huge amounts of biologically relevant data in a very short time. Although there are still many questions about what these data might mean for human risk assessment, it is reasonable to predict that the powerful computing systems currently available can and will be employed to discern patterns in this data and to begin to make more accurate predictions of human hazard and risk. These nonanimal approaches are already about as accurate as the animal test methods[32,33] so any improvement in predictive capacity will increase the advantage of the new nonanimal approaches over the current animal test methods.

The potential of the new approaches, exemplified by the ToxCast program, to improve toxicity testing and risk assessment can be estimated by looking at what has happened as a result of the Human Genome Project (HGP). It cost approximately $300 million to sequence the first human genome (the entire HGP cost being around $3.8 billion). Since the completion of the HGP in 2001, the cost of sequencing a human genome has dropped to a little more than $1,000 (a 300,000-fold improvement in cost per genome).[34] The potential economic and time benefits of switching to a new approach for not just toxicity testing but also a wide range of other biological research and development fields are just as promising as for the HGP.

The new nonanimal paradigm for risk assessment is already a viable alternative to animal test systems. First, there is the increasing power and availability of molecular measurement tools such as the new genomics "chips," which are able to probe the functioning of biological networks inside organisms, organs, tissues, and cells. Second, improvements in the robot systems at the NCGC described previously will increase their versatility and reliability. Third, the explosion of computational power, data-storage capacity, and information management tools is driving the development of sophisticated systems biology models. Fourth, the acceleration in the development of adequate in vitro test systems using human cells to look at specific control points in what are now termed "adverse outcome pathways" will further improve the versatility and reliability of this approach.[35]

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Fifth, an increasing amount of resources are being devoted to nonanimal and more efficient approaches by corporations (hundreds of millions of dollars in the past 30 years); by government agencies such as the U.S. Defense Advanced Research Projects Agency (DARPA), which recently invested $70 million to develop up to 10 "organs on chips"; and by European governments and companies, which have invested billions in the new Innovative Medicines Initiative (IMI).[36,37]

The Ethics of Toxicological Testing

It is widely agreed that the use of animals in studies that poison them to the point of death, or kill them for pathological studies if they have not yet died, is morally problematic, if not obviously wrong, all things considered. Today virtually everyone agrees that it would be preferable not to do toxicity studies in animals if they are unnecessary in light of available alternatives, and it is generally recognized that there are compelling scientific, economic, and practical arguments against continuing such animal studies as the new technologies come online and are refined to produce more predictive results. The real question now is *when* we should stop undertaking the animal testing that still occurs.

Regulators and toxicologists argue that we need to validate the new systems before abandoning animal testing. However, this argument begs two questions. First, animal studies have rarely been subjected to any validation, so why should they be given a free pass when the alternatives are not? One validation study conducted more than 40 years ago of the Draize eye irritancy test found serious problems with the test.[38] Second, what data should we use to validate the new tests? The human toxicity data are limited and not particularly useful. Meanwhile, the data derived from animals are not an adequate validation benchmark, because, instead of a test that predicts toxic risk in animals, we need one that predicts the risk in humans. So from any reasonable ethical perspective, we ought to accept the need to do the following:

1) End animal testing promptly (with a few possible exceptions)
2) Invest more heavily in the new paradigm outlined by the National Research Council in 2007 and then embraced by toxicologists in Europe, North America, and, increasingly, other parts of the world[39,40,41]
3) Begin to educate government regulators on the benefits and pitfalls of the new paradigm so that regulatory decisionmaking will take full advantage of it, leading to quick and more reliable policy decisions.

Conclusion

Toxicity studies on animals comprise somewhere between 5 and 15 percent of the overall use of animals in biomedical laboratories (that is, laboratories that conduct studies or tests of biological relevance to humans), and the proportion has been declining. We conduct such studies to protect humans, the environment, and animals from toxic hazards caused by the use of the 80,000 or so chemicals, including pharmaceutical and biological compounds, that are currently commercially available.

There is relatively little evidence demonstrating the effectiveness of such studies. We know that toxicity studies in animals lead to harms and suffering for many

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animals used, but we still know little about the extent or prevalence of such harms. There is now a developing consensus that animal tests are time consuming and not particularly effective in predicting harms to humans and the environment.[42,43] In the past decade, interest in moving away from animal tests and toward the use of quicker and cheaper alternative test systems has grown rapidly. Increasing numbers of toxicologists and regulatory officials now look to new technologies and the potential to refine and develop those new technologies in significant ways to predict the hazards and risks to humans and the environment caused by chemicals. Some still struggle to tweak existing animal tests so that they will be ethically improved and better predictors of, say, endocrine disrupting effects, but it is increasingly evident that animal studies are far from the best and certainly not the only way to assess the toxicity of the vast number of chemical substances that have already been developed.

Moral concerns will be an important factor—but are far from the only or the most important factor—in reducing our reliance on animal test data in upcoming years. I wholeheartedly endorse the moral campaigns by animal advocates since 1975, which have been a principal stimulus leading to the new approach being pursued today, but economic and efficiency issues will likely be at least as influential in driving us to a new paradigm for human hazard and risk assessment. This new paradigm will also be extraordinarily influential for general biomedical knowledge and science, because it will usher in a new era of understanding of the biological properties of small molecules (which constitute the majority of the 80,000 chemicals in commerce) and will lead to a much more efficient science of toxicology and to new insights in pharmacology. The prospect of having methods—which happen to be mainly nonanimal—that allow a quick and cheap evaluation of the biological effects of small molecules opens up tremendous opportunity for human safety and human therapeutic benefit.

The new adverse outcome pathway approach in toxicology will also be applied to drug development and human disease states. With more development, these approaches should help underpin the development of effective new drugs at a fraction of the cost we are seeing today (the latest research indicates that it now costs around $2.6 billion to produce each new drug entity[44]) and should also lead to exciting new therapeutic approaches for a range of human diseases. We are now witnessing the beginning of the end of animal testing for human safety and risk assessment, not just for environmental chemicals but also for drugs and therapeutics.

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