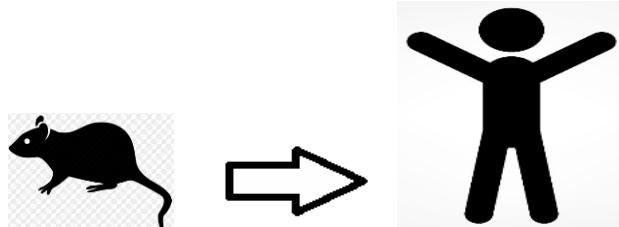


The Use of Animals in Toxicology & Safety Science

Despite significant recent advances in experimental techniques using cultured cells and tissues, including genetically engineered human cells, experiments using animals remain an important part of scientific research: providing experimental models to study disease, helping to develop and test new medicines and other forms of treatment and protecting the safety of people, animals and the environment.



Why are Toxicology Studies Done?

Toxicology and safety science aims to understand the potential effects of harmful substances on people, animals and the environment, *if* they were exposed to them. By understanding these types of effects, harmful exposures can be avoided, or levels of exposure can be regulated to those which are known to be safe. Enhancing our understanding of how chemicals interact with biological systems, knowing how the responses can vary in different species and understanding the impact of chemicals when they overload normal biological processes, are all key factors in developing safer products. Many species have common physiological processes and, therefore, the biochemical causes of classical types of toxicity (e.g. cyanide, lead, arsenic etc) are broadly translatable between species (*Hall et al 2015, Flora G et al 2012*). The experimental models which are used to understand and research the safety of chemical substances, including new medicines, are continually being improved and refined to ensure that they are as effective as possible at protecting living species and our environment from harmful effects.

How are Results from Toxicology Studies Used for Chemicals and Pesticides?

It is important to understand the safety to humans and to wildlife of chemicals which are used in the environment, including pesticides and biocides. Similarly, people need to be appropriately protected from chemicals to which they may be exposed in their working environment.

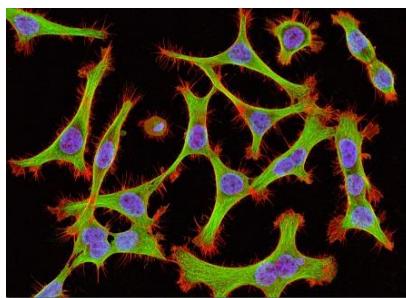
Once the potential harmful effects of a chemical are understood and the exposure level at which harmful effects are seen has been determined, a risk assessment can be conducted, and risk management processes can be planned and implemented. For chemicals, these commonly include calculation (using experimental data) of a maximum safe exposure level, an appropriate product classification, product safety labelling and, if necessary, legal restrictions are imposed on the way in which a chemical can be sold or used. The Government Agencies which regulate the sale and use of chemicals normally require animal safety (toxicology) studies to have been performed, *before* a product can be registered and approved for sale. For new pesticides, there are mandatory requirements in most Countries of the world, for safety (toxicology) studies to be conducted in animals, unless non-animal tests have been developed and shown to work reliably (*OECD, 2012*).

Advances in our understanding of the mechanisms by which chemicals can cause toxicity (their mode of action) is leading to more frequent use of non-animal, cellular and molecular experiments, to explore the key events in these pathways and thus, to better characterise the toxicological effects and improve risk assessments.

How are Results from Toxicology Studies Used for Medicines?

Experimental animal studies play an essential role in applying biological research to real problems in human and veterinary medicine. They allow new targets for disease intervention to be identified and potential new therapies, medical devices and surgical procedures to be tested. Initially, safety testing uses isolated cells, tissues or organs. To protect humans from serious forms of toxicity, there is an ethical need (and normally a legal requirement) to conduct experimental safety studies using a suitable experimental animal, before clinical trials in humans can take place (*World Medical Association 2013*). The data from animal experiments are frequently pivotal in deciding whether trials in humans should be allowed and, if so, what dose levels should be used, allowing for a margin of safety. Some toxicology studies in animals are usually performed *after* the first clinical trials: these include tests to detect the potential of a new medicine to malform a developing fetus, or tests to determine whether a new medicine has the potential to cause cancer.

Toxicology & Safety Studies Without Animal Experiments



Human Epithelial cells grown in a laboratory

Wherever possible, alternatives to the use of animals, such as *in silico* (computer modelling), *in chemico* (chemical reactions) and *in vitro* (bacteria, cell and tissue culture) experiments are used. Normally, if a new chemical, or a potential new medicine gives unfavourable results in these studies, no animal studies would be performed.

Non-animal studies are already being applied to test the safety of ingredients used in cosmetics. In certain parts of the world, including Europe, Israel and India, it is now illegal to market a cosmetic product containing a new ingredient that has been safety tested using animals. Several major international collaborative research projects are in progress to develop additional, non-animal experimental methods for use in safety assessment, or for other end-use tests - such as the batch release of vaccines. In the UK, the National Centre for the Replacement, Refinement and Reduction of Animals in Research (*NC3Rs* <https://www.nc3rs.org.uk/>) plays a major role, coordinating and promoting procedures to minimise the use of animals in research.

Ethical Principles: The 3Rs - *Reduction, Refinement and Replacement* of Animal Experiments and The Law on Animal Experiments

It is accepted good practice that scientists who use animal tests should apply the 3Rs principle to reduce the impact of research on animals (*Russell & Burch, 1959*). Implementing the 3Rs requires that, in every research proposal, animals are replaced with non-animal alternatives wherever possible, that the number of animals is reduced to the minimum needed to achieve the results sought, and that, for those animals which must be used, procedures are refined to minimise any possible pain or suffering.

The first legislation in the world to regulate animal experimentation was the UK Cruelty to Animals Act in 1876. It established a central governing body that reviewed and approved the use of animals in research. Subsequently, numerous countries in Europe adopted legislation to regulate research with animals. In the USA, the Animal Welfare Act was introduced as Federal Law in 1966, to regulate the treatment of animals in research (later amended in 1970 to include laboratory rodents and birds).

Public Information Article. British Toxicology Society <http://www.thebts.org/>

In 1998 the UK government also introduced further 'local' controls—that is, an Ethical Review Process at research institutions—to promote good animal welfare and humane science, by ensuring that the use of animals for experiments is justified. In 2000, the OECD published guidance on humane endpoints for animal tests, which stressed the importance of welfare considerations in all regulatory testing (*OECD Guidance No 19*).

In Summary

The responsible use of animals in experimental research to understand the potential of medicines or chemical substances to cause serious or irreversible forms of toxicity (and therefore to determine their safe use) is fundamental to help improve and protect human lives and the environment. It is an ethical imperative for *all* safety scientists to continue efforts to reduce the use of animals to the minimum extent necessary. As scientific knowledge advances, the goal to further minimise the use of animals will be achieved.

References

Hall A H, et. al. Eds 2015. Toxicology of Cyanides and Cyanogens: Experimental, applied and clinical aspects. ISBN:9781119978534 <https://onlinelibrary.wiley.com/doi/book/10.1002/9781118628966>

Flora, G et. al. 2012. Toxicity of lead: A review with recent updates. *Interdiscip Toxicol*. Jun; 5(2): 47–58.

OECD, 2012. Environment, Health and Safety Publications. Guidance document No. 116 on the conduct and design of chronic toxicity and carcinogenicity studies, supporting test guidelines 451, 452 and 453, 2nd Edition. <https://www.oecd-ilibrary.org/docserver/9789264221475-en.pdf?expires=1557271472&id=id&accname=guest&checksum=622E7E70B869677E662DC2A8ABE92211>

World Medical Association 2013. Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects, Section 17. <https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/>

NC3Rs <https://www.nc3rs.org.uk/>

Russell W.M.S. and R.L. Burch 1959. The Principles of Humane Experimental Technique. Methuen, London, UK. 238pp. http://altweb.jhsph.edu/pubs/books/humane_exp/het-toc.

OECD, 2000. Guidance Document No.19 The Recognition, Assessment and Use of Clinical Signs as Humane Endpoints. <https://www.humane-endpoints.info/images/56780863a7d49/OECD%20Guidance%20document.pdf>