



Lethal Business:

the use of animals in toxicity testing
An Animal Aid Report

Written by André Menache B.Sc. (HONS), BVSc MRCVS FRSH



Animal Aid

The Old Chapel, Bradford Street, Tonbridge, TN9 1AW

Tel: 01732 364546 info@animalaid.org.uk

www.animalaid.org.uk

Published by Animal Aid, November 2005

ISBN: 1-905327-04-8



Lethal Business:

the use of animals in toxicity testing An Animal Aid Report

Written by André Menache B.Sc. (HONS), BVSc MRCVS FRSH
Scientific consultant to Animal Aid

I	Summary	
2	Introduction	1
3	The scope of toxicity testing in the UK	2
4	Examples of toxicity testing	3
5	The legal requirement for animal testing	5
6	The 'scientific basis' for the selection of a rodent and non-rodent species	5
7	The rodent model	5
8	Selection of a non-rodent species	7
9	Drug safety testing and public health	8
10	Non-animal testing methodologies appropriate for regulatory toxicology	10
II	Conclusion	12

I Summary

This report investigates the scope and nature of toxicity testing in the UK involving animals. In addition to the serious welfare concerns of such experiments, animal testing is increasingly being criticised for its methodological

shortcomings. Modern non-animal methods that have already shown themselves to be relevant to human health and in gauging environmental impacts should therefore be promoted and adopted without delay.



2 Introduction

Toxicity is a measure of the degree to which something is poisonous. The study of poisons is known as toxicology. Toxicity testing ranks as one of the most extreme forms of deliberately-inflicted animal suffering, because death is often the endpoint of the experiment. Animals who do not die in the course of the experiment will be killed anyway, in order to study their tissues. In many tests, very high doses of test compound (often thousands of times more than any conceivable human exposure) are given so as to reveal possible adverse effects. Symptoms may include vomiting, diarrhoea, haemorrhage, breathing difficulties, severe irritation, seizures and, eventually, death. Long-term toxicity tests may result in liver damage, weight loss and tumours.

Toxicity testing is carried out in the UK for purposes of safety or efficacy of pharmaceutical preparations as well as of industrial chemicals. It accounted for nearly half a million animal procedures in 2003, or 16 per cent of the total. Mice, rats and fish were most often used. However, a whole range of animals are killed in such tests, ranging from chickens to rabbits and guinea pigs. In the field of medical drug testing, a rodent and a 'higher mammal' non-rodent species are required for regulatory purposes. The non-rodent species commonly used is the dog, but now, increasingly, monkeys are being used.

Toxicity tests usually involve force-feeding animals by gavage (a long tube pushed right down to the stomach – a very unpleasant experience) or injection, or both. In other 'procedures', the animals are forced to inhale vapour by sealing them in an air-tight chamber.

In addition to causing extreme suffering, the use of animals in such tests is exceedingly unreliable as a predictor of human toxicity, which raises serious public health questions regarding the relevance of such tests. During the middle ages, the king would often have his food tested for poison by the court jester – and not by the dogs. Even then, plain common sense

was sufficient to recognise the importance of species differences. The animal models used today do not reliably predict human outcomes, because of the vast differences between animal and human metabolism and lifespan. Equally, the sheer number and combinations of chemicals to which humans are exposed simultaneously is something that cannot be duplicated in animals in a laboratory setting. However, there are non-animal methods that could successfully be employed (see Section 10).

Today, we live in a sea of chemicals – around 100,000 of them – ranging from pharmaceutical drugs, food additives and pesticides, to air fresheners and deodorants. The potentially deleterious effects that these chemicals have on human health and the environment have not been well studied. Perhaps the most notable reason for this 'oversight' is the enormous economic burden of exposing millions of animals to thousands of individual chemicals over varying lengths of time, even years. Such tests typically involve single chemicals and will therefore not detect the effects of potentially dangerous *combinations* of chemicals (the so-called '*cocktail*' effect). In addition, it is a well known toxicological phenomenon that a pesticide may exert its most toxic effects at lower doses. Toxicopathologist, Dr Vyvyan Howard, has estimated that, in order to test the commonest thousand toxic chemicals in unique combinations of three, it would require at least 166 million different experiments (1). Even then, we still would have no way of knowing what of the resulting animal data was relevant to humans.

Animal welfare concerns aside, the current safety testing regime is seriously negligent with regard to its declared purpose of protecting public health.



B The scope of toxicity testing in the UK

According to Home Office figures for 2003, at least 16 per cent (or 448,000) of all procedures (i.e. experiments) were for toxicological purposes, and it was claimed that five out of every six of these were performed to conform to legal or regulatory requirements (2).

Table 1 Number of animals used in toxicological procedures in UK in 2003

Mouse	189,407
Rat	143,186
Guinea pig	12,376
Hamster	689
Other rodent	30
Rabbit	17,538
Cat	8
Dog	5,026
Ferret	7
Horse, donkey	84
Pig	1,693
Goat	1
Sheep	424
Cattle	1,119
Marmoset, tamarin monkey	398
Macaque monkey	3,143
Domestic fowl	10,724
Turkey	354
Quail	6,959
Other bird	320
Reptiles	1,467
Fish	52,766
Total	447,719

This figure may well be an underestimation. The complete picture is difficult to assess because of the unhelpful way in which the Home Office categorises different classes of experiment. Testing the safety of new pharmaceuticals accounted for 63% of all toxicity tests on animals in the UK during 2003 – or 280,585 animals.

Of the above total, not only were mice the most commonly used animals, but it was also they who bore the brunt of the acute lethal toxicity tests. Here, the animals experience a rapid onset of toxicity and a short, but severe, course of symptoms, leading to death. Painkillers are not used as they could interfere with the results. These experiments were used for safety, efficacy and quality control, mainly by the pharmaceutical industry. Rats were generally used in longer-term exposures, for example, reproductive system studies involving pharmaceutical products. Fish were largely used to study the effects of pollution, while rabbits were employed as living test tubes to detect product impurities for the pharmaceutical industry. Guinea pigs as well as mice were used to test products used in agriculture and industry that could cause skin irritation. Fowl were preferred for the safety testing of agricultural and pharmaceutical products.



4 Examples of toxicity testing

1. Botox testing in mice

Thousands of mice are still being killed every year in UK laboratories, for the safety testing of botulinum toxin, which is the active ingredient in the cosmetic preparation, botox, as well as in therapeutic products used for medical conditions, such as Parkinson's disease. This use of animals is a clear breach of the 1998 government ban on cosmetic product testing. In this case, the notoriously cruel LD50 test is used, in which 50 per cent of the test animals must die before the experiment can be concluded.

The botox testing scandal is further compounded by the fact that a key government-appointed testing laboratory – the National Institute for Biological Standards and Control (NIBSC) – employs a completely non-animal testing method for botulinum that annually spares the lives of an estimated 5,400 mice within the NIBSC alone. The test is known as the SNAP-25 method (3).

Despite the blatant flouting of the rule prohibiting animal testing of cosmetic products, the Home Office insists that no such licensing is allowed. This is technically correct ... but dishonest. While licences are granted for the testing of botulinum and, while it is claimed that all such tested botulinum is intended for medical use, the self-evident reality is that a great deal of it ends up being used for purely cosmetic purposes. The government knows this – as is made clear by answers to a series of Parliamentary Questions posed to Home Office Ministers by Michael Hancock MP in March 2005 (4).

The government made clear in its replies that it did permit botulinum tested under a therapeutic licence to be sold as a cosmetic product – but that the onus is on the doctor who prescribes its use for this purpose. This allows the government to defend itself against claims that cosmetic botox has not been tested and yet,

simultaneously, can insist that it has not licensed animal tests for cosmetic botox.

2. Vomiting shrews

Researchers at St George's Hospital Medical School, London, chose the house musk shrew as a model for studying nausea and vomiting in humans (a known side effect in people undergoing chemotherapy). It was observed, by chance, that some of the shrews spontaneously ate their own vomit. This observation persuaded the researchers to study vomiting in shrews, *unrelated to their chemotherapy-in-humans* experiments. Three groups of 16 shrews (specially bred at St George's) were forced to vomit, either through the effects of motion sickness, or else by being administered nicotine. The animals were subsequently killed with carbon dioxide, and then their necks were broken. This was done in order to study and weigh the stomach contents of each shrew. The researchers concluded that '*This curious behaviour observed under laboratory conditions, if replicated in the wild, may have significant ecological consequences for shrews*'.

Source: Potential energetic implications of emesis in the house musk shrew (Suncus murinus). Andrews PL, Friedman MI, Liu YL, Smith JE, Sims DW. (Department of Basic Medical Sciences, St George's Hospital Medical School, London). Physiology and Behaviour 2005; 84:519-524.

3. Inflamed livers in Beagles

Researchers in the Department of Pharmacology and Therapeutics at the University of Liverpool used beagle dogs and rats to study the adverse effects of an experimental anti-inflammatory drug. The drug was originally developed to treat inflammatory skin disease in humans, and appeared to work in mice. However, in subsequent (unpublished) experiments using rats and beagle dogs, the drug caused liver damage, and was therefore discontinued. The authors of the present study, nevertheless, were keen to



elucidate the mechanism by which the drug caused liver damage. Healthy adult rats and beagle dogs were injected with the drug and then killed so that their livers could be used to assess the effects of the drug. It was found that the drug damaged liver cells in both the rat and the dog. However, the researchers had difficulty in understanding the mechanism of cell toxicity, and could not explain why the drug should cause liver inflammation in dogs, but not in rats.

Source: Formation and protein binding of the acyl glucuronide of a leukotriene B antagonist (SB-209247): relation to species differences in hepatotoxicity. Kenny JR, Maggs JL, Tettey JN, Harrell AW, Parker SG, Clarke SE, Park BK. (Department of Pharmacology and Therapeutics, University of Liverpool). *Drug Metabolism and Disposition* 2005; 33:271-281.

4. Tumours in rats

Researchers at the Institute of Occupational Medicine in Edinburgh exposed 352 rats to a cancer-causing substance. Young (9-12 week) rats were divided into groups of 50 and injected with either cellulose or asbestos fibres. Although these fibres are normally associated with lung disease in humans, the animals were injected in their abdominal cavities to observe the body's response. The authors state that such studies had already been undertaken previously in 1992, 1995, 1996 and 1997. However, in this study, the amount of fibres injected was particularly large – so large, in fact, that the fibres were administered in three doses instead of one. Even the authors voiced concern about the volume of fibres. The experiment was allowed to run its course (up to 28 months) until nearly all the animals had died from advanced abdominal cancer with blood-stained abdominal fluid.

The authors concluded by saying that the study demonstrated that high doses of fibres are capable of producing tumours when injected into the abdominal cavity of rats.

Source: Tumorigenicity of cellulose fibers injected into the rat peritoneal cavity. Cullen RT, Miller BG, Clark S, Davis JM. (Institute of Occupational Medicine, Edinburgh). *Inhalation Toxicology* 2002; 14:685-703.

5. Chemical burns in pigs

Scientists in the Biomedical Sciences Department at the Ministry of Defence, Porton Down, used pigs to test the effects of a well-known corrosive chemical agent. Three Large White pigs were anaesthetised and then exposed to the effects of *Lewisite*. This chemical, known since 1918, is extremely toxic and can produce full-thickness (i.e. third-degree) burns when applied to the skin. Its effects have already been well documented in the scientific literature.

After exposure to the chemical, which produced severe skin blistering, the test animals were allowed to recover from the anaesthetic. Twenty-four hours later, all three pigs were killed by lethal injection, and tissue samples taken.

The researchers concluded that the test results were consistent with those reported by other scientists in 1994, 1989 and 2002. It was also concluded that the present study confirmed the use of the large white breed of pig as an 'appropriate model' for pursuing further such studies.

Source: Examination of Changes in Connective Tissue Macromolecular Components of Large White Pig Skin Following Application of Lewisite Vapour. Lindsay CD, Hambrook JL, Brown RF, Platt JC, Knight R, Rice P (Biomedical Sciences Department, Dstl Porton Down, Salisbury, Wiltshire) *Journal of Applied Toxicology* 2004; 24:37-46.



5 The legal requirement for animal testing

Animal testing is influenced by both national and EU legislation. Although the Home Office officially claims that all new drugs are required by law to undergo animal experiments (5), on closer examination, this would appear not to be the case. For example, the UK Medicines Act 1968 and other UK regulations do not specifically require animal tests (6).

The only piece of legislation that specifically refers to animal testing (Annex I of Directive 2001/83/EC) states that toxicity tests '*shall be carried out on two species of mammals one of which must be a non-rodent*'. However, this seemingly solid statement is tempered by article 7.2 of Directive 86/609/EEC, which states that an animal experiment must not be carried out if a non animal method could be used to provide the information in question (see Section on non-animal testing methods).

It must therefore be concluded that there are essentially no legal obstacles to the replacement of animals in toxicity testing.

6 The 'scientific basis' for the selection of a rodent and non-rodent species

The choice of rodents for the study of human toxicity can be traced back to the 1940s. The late Professor Dennis Parke, a former chief advisor on food safety to Unilever Corporation and advisor to the FDA (US Food and Drug Administration), reviewed how the humble rat came to be chosen, and whether or not the use of this animal as a 'standard' model was a sound choice: '*The wild rat was readily available and became the experimental animal, and*

this is how the drug safety industry began. Later on, inbred strains of rats were developed to enhance the uniformity of response, but there was little or no consideration at that time as to whether or not the rat was a scientifically appropriate surrogate species for man' (7).

7 The rodent model

The following two tables (on page 6) illustrate some of the species differences between rats and humans, rats and mice, and between different types of rats. There does not appear to be any biological trend or logical pattern that scientists can follow.

Tables 2 & 3 illustrate a clear lack of concordance with respect to several animal species, including humans. The similarity between rats and humans in regard to the lethal dose of *caffeine* proves to be the exception, rather than the rule. More significantly, the animal data can only be correlated with human data *in retrospect*, i.e. only *after* human exposure. Human data of lethal overdose are obtained from suicide attempts and accidental poisonings. For rare chemicals, the human values remain unknown.



Table 2 Species differences with respect to rodents and humans in toxicity testing Human Acute Lethal Doses (LDLO) and Animals LD50s (Oral)

Chemical	Humans LDLo* (mg/kg)	Rat	LD50 (mg/kg)		
			Mouse	Rabbit	Dog
Aniline	350	440	-	-	-
Amytal	43	560	-	575	-
Boric acid	640	2,660	3,450	-	-
Caffeine	192	192	620	-	-
Carbofuran	11	5	2	-	19
Lindane	840	125	-	130	120
Fenoflurazol	-	238	1,600	28	-
Cycloheximide	-	3	133	-	65
Aminopyrone	-	1,380	1,850	160	150

*(LO = lethal overdose)

Source: Adapted from Christenson and Luginbuhl 1975; Sunshine 1979.

In: The Cruel Deception, Robert Sharpe 1988, Thorsons.

Table 3 Intra-species variation with respect to rats

Drug	Lethal dose (LD50)	
	Young rat	Adult rat
Digitoxin (cardiac glycoside)	0.1mg/kg	Male
		Female
		76mg/kg
Amidephrine mesilate(vasoconstrictor)	Young rat	Adult rat
	3000mg/kg	36mg/kg
Isoproterenol (bronchodilator)	200g rat	600g rat
	800mg/kg	0.3mg/kg
Trifluoroperidol (neurotransmitter)	female rat	male rat
	140mg/kg	360mg/kg
Thiourea (industrial chemical)	Hopkin strain	Norway strain
	4mg/kg	1830mg/kg

*Note the massive anomalies throughout the above table - and, in particular, the difference in lethal dose simply on the basis of age *within the same species*.

Source: Zbinden G., Flury-Roversi M. (1981) Significance of the LD50-test for the toxicological evaluation of chemical substances, Archives of Toxicology, 47, 77-99.



8 Selection of a non-rodent species

The regulatory requirement for testing in two animal species (rodent and non-rodent) would appear to be as arbitrary as it is unscientific. Whereas the selection of a rodent as the first species is considered by both industry and regulatory authorities to be 'standard practice' (based on habit and considerations of convenience), the selection of the second species is much less so.

Although drug manufacturers are required to submit 'good data' to the regulatory authorities, the regulators are quite content to allow the company developing a new chemical product to choose its own testing strategy. Thus, the choice of a second, non-rodent species becomes something of a lottery – a beagle dog or a non-human primate (macaques or marmosets) may be just as acceptable as a minipig, or even a ferret (8). Given the unpredictable results of animal testing, as evidenced in the preceding tables, this *laissez faire* attitude on the part of the regulatory authorities is clearly not in keeping with their role of protectors of public health.

Dogs remain popular for purposes of regulatory toxicology because they are docile, easy to handle, and have been used so extensively that there is a vast amount of data on them. Ferrets would be more popular if they were not so awkward to inject or to take blood samples from. Minipigs are increasingly popular, but they can grow quite heavy – making them much more expensive than marmoset monkeys to dose with valuable test chemicals.

Indeed, there has been an increasing trend over the last few years to use marmosets. An enlightening paper (9) published by the Association of the British Pharmaceutical Industry (ABPI) makes a valiant attempt to pretend that the choice of marmoset is rooted in science, but it is abundantly clear that the real reasons are considerations of cost and convenience

for researchers. Marmosets weigh around 400g and are thus comparatively cheap to dose with valuable test compounds. Their small size also makes them easy to incarcerate in small cages or in inhalation chambers.

There is the added attraction of a relatively long lifespan (though short by human standards). This means that they can be used in chronic (long-term) toxicity studies – lasting up to several years. Marmosets are, furthermore, easy to breed in captivity, allowing drug companies, or their contract testing firms, to keep in-house colonies and avoid the controversy associated with importing macaques or other monkeys from abroad (e.g. China, journeys from which can last up to 58 hours). Their use also seems – so far – to have attracted less controversy than that of companion animals such as dogs.

As more firms opt for marmosets, their use is likely to increase further as there will be more data for comparisons. UK regulators (notably, the Medicines and Healthcare products Regulatory Agency) accept marmoset toxicity data quite readily, without querying their use. This is despite Home Office regulations stating that the use of non human primates is permissible only when there is no alternative animal 'model'. Whatever animal species is chosen, it is impossible to know whether it is a good 'model' for humans until we discover how humans react to the substance in question – by which point the animal data is clearly unnecessary!

It must be concluded that rodents, dogs and, increasingly, marmosets have become the species of choice for medical drug testing, simply because they are readily available and convenient to use.



9 Drug safety testing and public health

Despite the fact that regulatory requirements relating to testing in a rodent and a non-rodent species are being met, there is nevertheless a high incidence of adverse drug reactions (ADRs) in the human population. According to the British Medical Journal, five per cent of all hospital admissions are the result of ADRs (10) – and the annual number of people ultimately dying from ADRs translates into a total figure of 18,000 deaths – more than five times the number of people killed every year in road traffic accidents.

Significantly, human liver damage is the most frequent reason cited for withdrawal of an approved drug and accounts for more than 50% of cases of acute liver failure (11). This important phenomenon is, in no small measure, explained by scientific evidence strongly suggesting that *human liver damage has the poorest correlation with regulatory animal toxicity tests* (12).

Animals frequently receive very high doses of a test compound (often thousands of times more than any conceivable human exposure) in an attempt to determine whether the substance poses a health risk (to humans). A sad example is the *lifetime rodent bioassay (LRB)* for predicting human carcinogenicity. In this experiment, rats are exposed to potentially cancer-causing chemicals for as long as two years.

Defenders of the rodent bioassay claim that all known human carcinogens cause cancer in rodents. However, little attempt has been made to validate this assertion against human cancer data (13). Many toxicologists have expressed serious doubts as to the statistical relevance of the *LRB* (14). It is now acknowledged that this test yields many *false positives* (chemicals that cause cancer in rodents but not in humans). More significantly, it also yields *false negatives*. These are chemicals that, while harmless in rodents, are dangerous to people. To add to the confusion, using different *strains* of rats produces conflicting results (15).

Disturbingly, the *LRB* is still considered by regulators to be 'the standard' for predicting human carcinogenicity.

The food industry has not been slow to exploit the muddled results produced by the *LRB*. For example, the widely consumed artificial sweeteners *saccharine* and *aspartame* cause cancer in rodents (*saccharine* leads to bladder cancer, and *aspartame* to leukaemias). **The government, nevertheless, permits these products to be mass marketed because it has allowed itself to be convinced by the food industry that the animal tests are irrelevant.**

We are repeatedly told that such tests are 'necessary' – only for them to be discounted when their results are commercially inconvenient. What is the general public to make of this? Should animal tests be trusted? Of equal significance is whether the health authorities can be trusted.

The potentially negative implications of such data for public health do not stop there. Regulators not only allow industry to back their health claims with questionable animal data, but they also allow industry's 'experts' to determine how much of a chemical can be 'safely' consumed. This accepted volume is referred to as the *ADI* – *the acceptable daily intake*. It is typically expressed in mg/kg/day. The *ADI* does not take into account differences between individuals with respect to age, gender, weight, allergies, etc.

The *ADI* dosage is derived from data emerging from animal tests, to which adjustments are made in order to incorporate a safety factor. Usually, this means the original 'safe dose' being stepped up by a multiple of ten to account for intraspecies sensitivity (individual variation within the same species), interspecies difference (between species), and other factors of concern (completeness of data). The appropriateness of this arbitrary 'multiple of 10' has, understandably, been seriously questioned. Professor Frederick vom Saal at the University of Missouri-Columbia was quoted by *Nature* as saying: '*The evidence is that there can be as much as a 1,000-fold, or greater, range of responses to these chemicals in different strains of mice. The regulatory default assumption of a ten-fold*



correction or safety factor for genetic variability is completely out of touch with the data' (16).

Not surprisingly, when pressed to make a scientific case for animal tests, not even the Department of Health (DoH) can muster a plausible body of evidence. As part of its 2002 inquiry into Animals in Scientific Procedures, the House of Lords Select Committee asked the DoH to provide published scientific papers that support the validity of toxicity tests on animals. One of the papers (17) submitted by the DoH actually lists several reasons why data obtained from animals are usually not predictive of human effects. One difficulty is that *'the life span of humans is from 4.4 to 66 times that of common test species. Thus, there is generally a much longer time available for many toxicities to be expressed or developed in people than in test animals'.*

Another (18) contains this damaging admission: 'Two reviews addressed those drug cases where the clinical (human) toxicity was so severe as to lead to withdrawal from marketing in the approximate period 1960 – 1990... In one report, only 4 of 24 cases were predictable from animal data; in the other report, only 6 of 114 clinical toxicities had animal correlates.' **Given the lack of predictive value of animal tests, it is no wonder that adverse drug reactions are now the fourth leading cause of death in the UK, after heart disease, cancer and stroke! (19)**

Equally, it should come as no surprise that, in 2004, Home Office Minister, Caroline Flint MP, during an answer to a parliamentary question, stated: '**The Home Office has not commissioned or evaluated any formal research on the efficacy of animal experiments.**' When pressed by Michael Hancock MP about the future, instead of trying to undo the damage, the government dug itself even deeper into its hole by admitting that **it had no plans to commission such a study (20).**

REACH (Registration, Evaluation and Authorisation of Chemicals)

Media reports throughout 2004 and 2005 have suggested that the chemical industry

is being brought to heel by a timely proposal put forward by the EU, entitled REACH. In principle, EU authorities are right in wanting to assess 30,000 (tailored down from an original figure of 100,000) man-made chemicals for their adverse effects on human health and the environment. However, the prospect that this assessment will not be completed for several decades at least, and will involve a very large number (many millions) of animals, is cause for serious concern.

In January 2005, the European Parliament (EP) began its formal consideration of REACH at a public hearing. Three main committees of the EP (environment, industry and internal markets) reviewed REACH in detail, including 1000 tabled amendments. The EP first reading was expected to be completed with the Plenary (whole Parliament) vote during the week 14 – 17 November 2005, to be followed by a second reading by as early as April/May 2006. Barring any major delays, these EU regulations could become law in late 2006. However, there is likely to be a time lag between entry into force of these regulations and their implementation, ranging from three to 11 years, based on considerations such as production volume and public health risk.

Caroline Lucas MEP has stated: '*As a Member of the European Parliament, I have become increasingly aware of the threat posed by chemicals in our food, our homes and the environment. Throughout discussions of the European Commission's proposal for a new regulatory regime for chemicals (REACH), I have argued that the protection of human health and the environment is of paramount importance. At the same time, however, I have made the case that this does not have to lead to yet more cruel, outdated and inefficient animal tests. To the contrary, the new drive for safer chemicals can be used to generate new momentum for the use and development of non-animal testing strategies' (21).*



▣ Non-animal testing methodologies appropriate for regulatory toxicology

Ultimately, and not surprisingly, the best model for the study of humans is the human being. What follows are examples of non-invasive, human-based methodologies for toxicity testing. It is these, and similar systems, that should become the focus of attention and investment for industry and regulators. It is both noteworthy and disturbing to see how far behind the US the UK position is, in terms of progress towards regulatory acceptance of these methodologies (22, 23). There are, however, signs that some cooperation is taking place across the Atlantic on the issue of database development (24).

Toxicogenomics

Toxicogenomics is a modern scientific discipline that combines knowledge of toxicology and gene function. It can be used to obtain species-specific data that can be applied to any living cell system (plant, animal or human). In addition, toxicogenomics can be employed to study any chemical, whether it is a food additive, a pesticide, or a medical drug. When used in combination with high throughput screening methods, it is possible to study a large number of chemicals and to generate vast quantities of data with respect to possible cell damage. The results of these tests can be obtained in 24 – 48 hours. Animal tests often require up to two years to complete. Toxicogenomics is already recognised as an important adjunct for the assessment of toxic risk in humans in the USA and in Japan (25).

'Toxicogenomics applies genomics (the study of genes) concepts and technologies to study the adverse effects of chemicals. These studies use global gene expression analyses to detect expression changes that influence, predict, or help define drug toxicity. Technological advances have enabled scientists to simultaneously analyse thousands of genes of several species, including humans and rodents, quickly and in a reproducible manner. In short, the technology now exists to potentially revolutionise toxicity testing' (26).

Pharmacogenetics

Pharmacogenetics is the study of genetic factors that influence an organism's reaction to a drug. It takes advantage of knowledge from the human genome project and modern gene screening techniques. A report published by the Nuffield Council on Bioethics in September 2003 provides a good insight into this non-animal methodology and its specific application to humans: 'People often respond differently to the same medicine. Few medicines are effective for everyone; all may cause adverse reactions and occasionally death. Research in pharmacogenetics investigates how differences in our genes can affect the way in which we respond to medicines' (27).

QSAR

Quantitative structure-activity relationships (QSAR) correlate the structure or property of a chemical compound with its potential biological activities. For example, novel substances can be rapidly screened on the basis of their chemical structure, and compared with known existing compounds already in use. With the help of modern computers, QSAR currently are being applied in many disciplines, with many pertaining to drug design and environmental risk assessment (28).



Microdosing

Microdosing, or 'Phase 0' studies, involves the administration to human subjects of tiny amounts (sub-therapeutic or 'nanodose' concentrations) of an experimental drug. The fate of the drug in the human body can be tracked by means of radioactive labelling. The tiny dose of drug given is approximately one million fold lower than the recommended daily dose in patients and therefore significantly reduces the risk of adverse drug reactions (29).

Donated human tissues

There are more than 200 different cell types in the human body, all of which are available from UK human tissue banks, making it possible to focus our research on human cells, instead of animal cells. In addition to cell cultures, the use of human organ slices (in particular, the human liver) represents another important adjunct to the field of modern toxicology (30). Studying human organs brings scientists another step closer to understanding human health and disease. Although the isolated organ still falls short of a whole, living system, it nevertheless yields information relevant to the species in question – human beings. In addition, human patients can be studied non-invasively to reveal whole body function, and post-mortem examinations of deceased individuals can yield significant amounts of additional information.

**Non-animal testing methodologies
appropriate for regulatory toxicology**



II Conclusion

'The goal of toxicology is the assessment of possible risk to man' (31).

An issue underlying the whole question of safety testing is the perception that good health is largely dependent on a constant stream of new medical drugs coming onto the market. The reality of the situation is very different. According to the World Health Organisation, most of us could get by quite happily with a list of just 350 essential drugs. This core list presents the most efficacious, safe and cost-effective medicines for priority conditions (32). The pharmaceutical industry thinks otherwise – the British National Formulary lists more than 10,000 different medical drugs licensed for use in the UK.

It is perhaps this state of affairs that prompted a 2004 House of Commons Health Select Committee to investigate the marketing practices of the pharmaceutical industry. At the hearings, expert witnesses testified that 90% of new drugs brought on to the market were simply '*me-too*' – in other words, products that are not significantly safer or more effective than already existing drugs in the same class (33).

This unhealthy situation is made worse by the fact that we are all exposed to a cocktail of chemicals through the air we breathe, the food we eat and the water we drink. Very few of these chemicals have been tested for adverse health effects, although some are already known to be highly toxic (34).

This proliferation of unnecessary and often toxic chemicals of itself requires urgent political action. Meanwhile, common sense and the need to protect public health dictate that industry and the regulatory authorities work towards adopting a human-based, methodologically sound approach to toxicity testing.



References

1. **Howard V**, 'Synergistic effects of chemical mixtures – can we rely on traditional toxicology?' 'The Ecologist, Volume 27, No. 5, September/October 1997,
2. **HO** 'Statistics of Scientific Procedures on Living Animals, 2003.
3. **Sesardic D**. Microbiology, 1997 Oct;143 (Pt 10):3337-47.
4. Home Office response to PQ by **Michael Hancock MP**, 9 March 2005.
5. **Andy Burnham MP** in letter to Home Office, 21 July 2005.
6. BUAV campaign report – summer 2004.
7. **Parke D**. Ethical Aspects of the Safety of Medicines and other Social Chemicals. Science and Engineering Ethics, vol.1, issue 3, 1995.
8. **Broadhead CL et al**. In: Animal Procedures Committee report, December 2002.
9. **Smith D, Trennery P, Farningham D, Klapwijk J**, The selection of marmoset monkeys (*Callithrix jacchus*) in pharmaceutical toxicology. (AstraZeneca and Glaxo SmithKline), Lab Anim 2001 35 (2):117-30.
10. **Pirmohamed M, et al**. *BMJ* 2004;329:15-19.
11. **Lee WM**. *N Engl J Med* 2003;349:474-485.
12. **Xu J**. *Chemico-Biological Interactions* 2004;150(1):115-28.
13. **Ennever F, Lave L**. Implications of the lack of accuracy of the lifetime rodent bioassay for predicting human carcinogenicity. *Regulatory Toxicology and Pharmacology* 2003, vol. 38: 52-57.
14. **Ennever F, Lave L**. Implications of the lack of accuracy of the lifetime rodent bioassay for predicting human carcinogenicity. *Regulatory Toxicology and Pharmacology* 2003, vol. 38: 52-57.
15. **Ennever F, Lave L**. Implications of the lack of accuracy of the lifetime rodent bioassay for predicting human carcinogenicity. *Regulatory Toxicology and Pharmacology* 2003, vol. 38: 52-57.
16. **vom Saal F**. *Nature* vol. 409, January 18, 2001.
17. **Gad SC**, 1990. Model Selection in Toxicology: Principles and Practice, *Journal of the Am. Coll. of Toxicol.*, 3, 291-302.
18. **Olsen H et al**, 2000. Concordance of the Toxicity of Pharmaceuticals in Humans and Animals, *Regulatory Toxicology and Pharmacology*, 32, 56-57.
19. **Lazarou J, Pomeranz BH, Corey PN**, Incidence of Adverse Drug Reactions in hospitalised patients: a meta-analysis of prospective studies. *Journal of the American Medical Association* 1998; 279 (15), 1200-1205.
20. Home Office response to PQ by **Michael Hancock MP**, 25 March 2004.
21. **Caroline Lucas MEP** in: Endocrine disrupting chemicals: a non-animal approach. BUAV report 2004 by Dr Gill Langley.
22. **Freeman K**. *Environ Health Perspect* 2004;112(12):A678-85.
23. **Freuh FW**. *Environ Health Perspect* 2004;112(12):A663-4.
24. **Mattes WB**. *Environ Health Perspect* 2004;112(12):495-505
25. International Programme on Chemical Safety (IPCS) – toxicogenomics and the risk assessment of chemicals for the protection of human health. Held at the Federal Institute for Risk Assessment, Berlin, Germany 17-19 November 2003.
26. **Suter L**. *Chem Biol* 2004;11(2):161-71
27. Nuffield Council on Bioethics Report, September 2003.
28. www.netsci.org/Science/Compchem/feature12.html
29. www.laboratorytalk.com/news/pha/pha117.html
30. **Vickers A, Fisher R**. *Chemico-Biological Interactions* 2004;150:87-96.
31. **Suter L**. *Chem Biol* 2004;11(2):161-71
32. www.who.int/medicines/publications/essentialmedicines/en/
33. www.publications.parliament.uk/pa/cm200405/cmselect/cmhealth/
34. WWF-UK National Biomonitoring Survey 2003.

Written by André Menache B.Sc. (HONS), BVSc MRCVS FRSH
Scientific consultant to Animal Aid

**Animal Aid exposes and campaigns
peacefully against all animal abuse,
and promotes a cruelty-free lifestyle**



Animal Aid
The Old Chapel, Bradford Street, Tonbridge, TN9 1AW
Tel: 01732 364546 info@animalaid.org.uk
www.animalaid.org.uk

Published by Animal Aid, November 2005
ISBN: 1-905327-04-8