

Primate Testing in Europe



A report on the use of primates in regulatory testing in a typical European commercial testing laboratory

- Monkey supply and transport
- Life and death in the laboratory
- The experiments
- The alternatives

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Our Background

Animal Defenders International (ADI), founded in 1990 and with offices in London, San Francisco and Bogota, represents the National Anti-Vivisection Society (NAVS) (founded 1875) and its scientific research wing, the Lord Dowding Fund (LDF) (founded 1974) in the international arena. The three organisations are active on a range of animal protection and conservation issues worldwide, with their respective missions to: conserve and protect animals and the environment; work for and end to the use of animals in research; promote and fund non-animal scientific and medical research. The work of the three groups includes research, investigations, publishing of technical reports, educational materials, and briefings for governments. The LDF provides funds for scientists conducting non-animal scientific and medical research, with an annual research spend of circa £300,000/€320,107.

Summary

With the European Commission's proposed new Directive to replace Directive 86/609 on the use of animals for scientific purposes now in discussion in the European Parliament, it is important to study the use of primates in regulatory and commercial testing as well as academic research within the European Union. The main focus of this report is the use of primates in regulatory testing. 10,000 primates are used in research and testing in the EU each year, 70% of this is regulatory and commercial product testing.

In order to gain a first-hand understanding of day-to-day work and animal care practices in a typical European contract testing laboratory, we arranged for an investigator to work as an animal technician in the primate unit at Huntingdon Life Sciences, Cambridgeshire, UK.

Although much has been written about Huntingdon Life Sciences (HLS), we feel it is important to keep in mind that this is a typical European regulatory testing facility and that the accommodation and animal care, and the experiments we describe in this report, should not be dismissed as a 'rogue' case.

HLS is perhaps the most heavily scrutinised animal laboratory in Europe, having previously been exposed for falsifying data and animal cruelty (for which staff were subsequently convicted), and subsequently being threatened by the authorities with withdrawal of its licence²²¹. As a result, the company's shares crashed. Ten years later, the company boasts annual sales of £130million/€137million and £30million/€31.5million in profits. HLS clients, who commission experiments in order to launch new products onto the market, include the world's largest pharmaceutical and chemical companies with profits running into the billions. The UK's Ministry of Defence is a client. This is a wealthy industry, with wealthy clients.

In contrast, the monkeys used to test the new compounds huddle in small windowless rooms or small cages – starved of their home world, space, family, interest and stimulation and the kiss of the sun or a breeze on their cheeks.

This report and the accompanying DVD 'Save the Primates' reveals the standard set for welfare following under the UK's Animal (Scientific Procedures) Act 1986 and EC Directive 86/609.

Likewise, the Vietnamese primate supplier included in this report has been scrutinised by UK licensing authorities, even warned about its standards, to little or no avail. The impotency of EU regulation and the laws of Member States when it comes to setting standards in these institutions thousands of miles away is all too vivid.

We also examine the failure of the adoption of modern scientific techniques to replace animals. More alternatives are available than ever before, but primate experiments are rising. The casual acceptance and defence of animal experimentation has become a roadblock to progress. Yet when pressure is applied, as with the Cosmetics Directive or with REACH, the replacements are found.

Political and Public Support for Replacement of Primate Tests

European Directive 86/609 governing the use of animals in research in the European Union is now over twenty years old. The new European Commission proposal for a new directive is the first major overhaul since 1986. ADI, NAVS and the LDF have jointly published a series of proposals ('Vision for Europe') to improve and update the legislation. This includes the introduction of periodic reviews and a timetable to phase out the use of primates in research.

Working towards an end to the use of primates in research would follow through on the commitment originally expressed in Directive 86/609, over twenty years ago. **ADI, NAVS and LDF believe that it is time for this commitment to be fulfilled.**





Monkey number 88 peers from a cage at Huntingdon Life Sciences, one of the largest animal testing facilities in Europe.

Political and public support for replacement of primate tests

20 years on

The law has not kept pace with developments in science and technology. During the 22 years since Directive 86/609/EEC came into effect, the world has seen many changes:

- The digital age and the World Wide Web; communication and research tools changed our ability to share knowledge
- Sophisticated imaging technology - including brain and full body imaging
- Creation of the first virtual organs
- Introduction of microsurgical techniques and keyhole surgery
- Advances in biotechnology
- DNA chips
- Transgenic animals and cloning
- Intelligent databases and modelling systems
- New mobile communication technology, allowing transfers of sound, text, pictures and moving images
- Videotape replaced film, then DVD replaced video tape, now we download, and next...

Thus, scientific and technological developments capable of replacing the use of primates in both regulatory (safety) testing and academic research continue to advance at a pace which has left legislation behind. These developments have the advantage of providing data directly applicable to humans, and they represent the cutting edge of science. Adoption of these high-level technologies would position Europe as the world leader in science.

Any new Directive on the use of animals for scientific purposes must therefore include thematic, periodic reviews involving all stakeholders to focus on implementation of advanced techniques and advances in knowledge to help to keep the legislation up-to-date.

Making a special case for non-human primates

Members of the European Parliament and European citizens have identified that there is a strong ethical, scientific and conservation case for phasing out the use of non-human primates in regulatory testing (required for products to be put on the market) and in academic/fundamental research.

All primate species show high levels of intelligence, are dextrous, good at problem solving, behave co-operatively and have extensive social structures with components of culture. Rhesus macaque monkeys have proved themselves capable of learning rudimentary arithmetic, to think using symbols and have demonstrated 'theory of mind' – how to reason about what others think – a cognitive ability previously considered paramount to human beings. Both chimpanzees and orangutans have shown an awareness of self. Humans share more than 90% of our DNA with the majority of non-human primates.

Various non-human primate species have expressed emotions such as affection, caring, empathy, humour, anger, sadness, jealousy, and courtship behaviour similar to humans. Some gestures and behaviours are similar to humans, too, such as the way that they greet and play with each other. They enjoy close family bonds, and forge life-long friendships. Chimpanzees in particular display a range of postures and gestures similar to humans, such as greeting one another with kisses and embraces, holding hands, and tickling and reassuring each other. Chimpanzees and gorillas have been taught to communicate with humans using American Sign Language, and they have passed this skill on to the next generation. Various species of primates have been shown to learn by observing each other's behaviour, including tool use, fishing, and other activities.

All these attributes are significant because they explain why primates can be harmed not just physically, but through mental and emotional distress. This harm can be caused by capture, transport, isolation or barren environments.

We are primates. We know that they can suffer as we would.

Species differences

The similarities between ourselves and the non-human primates has caused some to argue that this justifies their use in scientific research. However this argument fails on scientific, ethical and conservation grounds. In nature, we can see the richness of diversity that just a small percentage of difference in DNA has made. There are fundamental differences at the cellular, genetic and immune system level which we ignore at our peril, as they make the results from primate tests unreliable for humans.

Political and public support for replacement of primate tests

These differences were illustrated when in the UK, test drug TGN1412 caused terrible, almost fatal, and permanent side effects in human volunteers. Yet the drug had been given to laboratory monkeys in doses 500 times that given to the volunteers, without side effects. Now many agree that this disaster could have been avoided by using advanced technology – microdosing (see later).

Researchers in Denmark and the USA compared genes found in humans to their equivalent genes in chimpanzees. They found that the genes which differ the most between humans and chimpanzees are those related to immune defence and cancer development. They also identified that the genes which are most similar between humans and chimpanzees are those which are expressed in the brain. This work has drawn attention to the misleading nature of primate testing, as results obtain from tests on primates for drugs, toxicity, disease and cancer would be inaccurate when applied to humans.¹

Furthermore the assumption that animal, especially primate research is somehow vital for human health has never been properly put to the test through systematic and retrospective scientific reviews. A growing number of reports suggest that, far from reliable, animal models are untrustworthy and should be replaced by scientifically advanced alternative techniques.

Advances in science and technology provide non-animal techniques that are faster, more accurate and of direct relevance to people. Animal research on the other hand is outdated and suffers from the flaw that all species respond differently to substances. **Studies have shown differences between humans and laboratory monkeys, on average, a third of the time.**

Threats to the existence of non-human primates

The case for conservation of non-human primates is weakened by the trade for European laboratories. New studies have found that a third²⁰ of primate species are in danger of being wiped off the face of the earth because of human exploitation. As governments in primate home ranges make desperate efforts to prevent the poor and hungry eating some species to oblivion, the western research community demands the right to take these species for unnecessary and unreliable experiments, when alternatives are available.

Furthermore European authorities can do little to influence the standard of welfare or the breeding programmes at foreign suppliers, which means that captive breeding facilities abroad can make up their stocks from wild populations.

The DVD accompanying this report highlights the **ecological damage and suffering to primates caused by the capture of owl monkeys in South America for malaria research**. Research which has received strong scientific criticism.

It is vital that Europe becomes the standard-bearer and leads the world on this issue, in order to influence foreign governments.

The unethical and short-sighted nature of snatching animals from the wild, as well as the suffering it causes, was acknowledged in EU Directive 86/609/EEC on animal experiments, over twenty years ago. **Nevertheless, an estimated 10% of primates in EU labs still come from the wild. Good intent has not been enough. A clear end to this trade is needed.**

Political and Public Opinion

In 2002 the European Parliament adopted this policy, *“the need for the continued use of non-human primates in research and testing should be critically evaluated in the light of scientific knowledge, with the intention of reducing and eventually ending their use”²*.

In 2005, at the World Congress on Alternatives, animal welfare, conservation and protection groups made a declaration on primate experiments. This was later expanded into the Berlin Declaration, which has now been signed by over 70 international animal protection groups (with combined supporters approaching 2 million people), together with many prominent individuals as well as members of the scientific community. The Declaration reads,

“Animal protection organisations and scientists have united to call for an end to the use of non-human primates in biomedical research and testing. We urge governments, regulators, industry, scientists and research funders worldwide to accept the need to end primate use as a legitimate and essential goal; to make achieving this goal a high priority; and work together to facilitate this. In particular, we believe there must be an immediate, internationally co-ordinated effort to bring all non-human primate experiments to an end”³.

The European Federation of Pharmaceutical Industries and Association *“supports current restrictions for the use of*



An animal technician walks past an immobilised monkey strapped into a restraint chair during an inhalation experiment.

Great Apes” and encourage “*European initiatives aiming at eliminating the need for NHP [non-human primates]*”⁴.

On the subject of toxicology, which represents 70% of primate use in the EU, the UK’s National Centre for the 3Rs (NC3Rs) and the Association of the British Pharmaceutical Industry (ABPI) have concluded, “*there are no regulatory guidelines that specifically require the use of primates and there is scope to review the scientific rationale for their use*”⁵.

An end to the use of primates in research would receive wide public support:

80% of respondents to the European Commission’s public consultation on the revision of Directive 86/609/EEC responded that the use of primates in laboratories is ‘not acceptable’. The awareness of primate suffering in laboratories is very high among the public in Europe and is a source of widespread concern.

In 2007, 433 Members of the European Parliament – the majority – signed Written Declaration 40, calling for the Commission, the Council of Ministers and the Parliament to use the revision process of Directive 86/609/EEC to:

- (a) make ending the use of apes and wild-caught monkeys in scientific experiments an urgent priority
- (b) establish a timetable for replacing the use of all primates in scientific experiments with alternatives

Written Declaration 40/2007 had received unprecedented cross-party support, with every Member State represented. It included prominent Europeans including former government ministers.

Tests on non-human primates: legal requirements

Huntingdon Life Sciences

Huntingdon Life Sciences is a major European contract testing laboratory, conducting toxicological (safety) tests on behalf of a range of clients who include manufacturers of drugs, chemicals, and other products. As mentioned earlier, regulatory testing represents approximately 70% of the 10,000 primates used in European laboratories each year, it is therefore important to study this sector of the animal testing industry (see Investigation section).

Tests on non-human primates: legal requirements

The use of primates in laboratories can be placed into two broad categories: commercial and regulatory testing (toxicology, also called safety tests), 'regulatory' are standardised and required for permission to be given for a product to be sold on the market, and academic (or fundamental) research, which is varied in nature and includes a range of experiments in the fields of biology, neurology, biochemistry, physiology, psychology and more.

There are no specific legal requirements for the use of primates in regulatory testing. European Council Directive 2001/83/EC requires two mammalian species to be used in regulatory testing, one of which should be other than a rodent⁶. Like dogs, non-human primate species are therefore used at the end of the testing strategy.

The UK's Animals (Scientific Procedures) Act 1986 (ASPA) is the legislation that brings Directive 86/609/EEC into effect in the UK. The UK Home Office issues a Code of Practice for the Housing and Care of Animals used in Scientific Procedures, under the authority of the Act. The UK requires that primates should only be used if no other species is suitable or practicable, and also that **"any use of non-human primates must be specifically justified"**. The Home Office emphasises that the criteria for selection of the second species include regulatory, scientific and ethical requirements⁷.

It is of concern that regulatory tests conducted by contract testing laboratories, on behalf of clients such as drug



A long way from home: A monkey recently imported from Vietnam inside the HLS J06 stock colony.

Drug development and safety testing using animals

companies, are not scrutinised in advance by the Home Office on a case-by-case basis. Project licences for these companies are authorised for **groups** of chemicals or drugs - avoiding the need for project authorisation for each product. This means that the scrutiny of the proposal to use animals is not undertaken.

Not only does this mean less scrutiny, but it means that less information is reviewed and held by the national authority on those experiments. The reports of the studies of regulatory and commercial animal tests are the property of the customer and therefore the authority does not have access to full information. This can lead to cases of unexpected suffering or occurrences that are not fully reported to the authority (NAVS & UK Home Office discussions, Inveresk Laboratories, 2005).

Group authorisations have been proposed for the new Directive currently under discussion at the European Parliament, and should be opposed.

Primate use has been rising, since the introduction of the new generation of so-called 'biological' products: In their report on the use of non-human primates in the development of monoclonal antibodies, the UK National Centre for the 3Rs (NC3Rs), highlights the issues *"Four main areas for investigation have been identified, including toxicology, pharmacokinetics (PK), drug dependency and biologicals. These... reflect the differing drivers for primate use from regulatory requirements to emerging technologies and the opportunities for reducing this use. The use of primates in the development of biologicals was a timely area for review given the increasing number of biological products in the pharmaceutical pipeline, the specific challenges faced in providing preclinical data and the implications for primate use"*⁸.

Academic experiments in universities (e.g. neurology, psychology, physiology, biochemistry) is another large area of primate use. There are no regulatory requirements for these academic experiments, so this is field where replacement could be very rapid.

Due to the varied nature of the experiments, a different approach would be needed for different fields of research, but this could be achieved through expert consultation and a focussed, technical review, managed by the Commission, under the new Directive.

These studies cause extreme suffering for example, brain research can include implanting electrodes and other equipment into the animals' heads, and the restraint involved to make recordings, as we shall show later, causes immense stress in primates. Often this so-called 'fundamental' research does not describe any potential application for human benefit.

Such experiments can be replaced by advances in modern scanning techniques such as fMRI and MEG, which are enabling non-invasive neuroimaging of the *human* brain, providing unprecedented understanding of mental illness, neurodegenerative diseases, vision, hearing, speech, pain and more. This provides data of direct relevance to patients, who can be asked to describe how they feel.

In 2008, a meeting at the European Parliament was presented with a comparison of data from scanning studies of human patients and electrodes implanted in the heads of monkeys. **The same level of data was obtained** – yet importantly one set of data was of direct relevance to people.

Drug development and safety testing using animals

The fundamental flaw of using animal test results to establish safety for humans is that of species differences. All species react differently to drugs and chemicals, because of the differences in genetics and biology, and many of these differences are well known. In addition, biochemical changes in the animals' bodies as a result of the stress of being used in the laboratory can also affect test outcomes. The development and use of advanced non-animal techniques therefore offers improved scientific method, and improved results, more relevant to humans.

The way a drug travels through the body – the rate and route by which it breaks down and moves through the body, before being excreted – is crucial. This is referred to as the drug's ADME (absorption, distribution, metabolism and excretion). Our genes, and other factors, influence the ADME of a drug. For this reason, despite the similarities between humans and the other primates, the small but key genetic differences between ourselves and non-human primates are hugely important in drug development and testing.

A review of animal use in drug development concluded *"Some species of experimental animals have such unique mechanisms of developing toxicity that extrapolation of such toxicity assessments to the human situation would be fraudulent"*⁹. A study of data from the rat, dog, monkey and human reported that *"the monkey overall tended to be the most similar to human, with only 32 of the 103 compounds (31%) in a different clearance category compared with humans"*¹⁰. **Therefore the primate model is different nearly a third of the time.**

Advanced techniques to replace use of primates

Researchers have recently commented, “experimental animals sometimes show significant species differences in the oral BA [when a substance is in a form that allows it to be metabolized] of drugs that might lead to the erroneous prediction of the BA in humans”¹.

Others have commented: “The many intrinsic differences in the ADME processes between animals and humans make extrapolation of animal data very difficult”, furthermore, “in the past 30 years, pharmacokineticists have failed to find an animal species in which the ADME processes of drugs are consistently the same as those in humans. In fact, it can be presumed that such an animal species will never be found”².

Use of data from primates has been criticised: “despite the similarities in monkey and human absorption kinetics, marked differences are found in oral bioavailability (lower in monkey) as well as in total and non-renal plasma clearances (both higher in monkey). ... caution should be exercised in extrapolating data obtained in monkeys as it may not predict that in humans”³.

Differences between humans and the cynomolgus macaque (*macaca fascicularis*) used at HLS in drug and vaccine testing and development are relevant to this discussion:

- Certain genes (cytochrome) create enzymes which are important in the metabolism of drugs yet there are differences between humans and the cynomolgus monkey. “Gene and protein expression of CYP2C76 was confirmed in the liver of cynomolgus and rhesus monkeys but not in humans or the great apes”⁴. This gene is “a major CYP2C in the monkey liver” and “CYP2C76 contributes to overall drug-metabolising activity in the monkey liver”⁴. A later paper by the same author concluded “Cynomolgus monkey CYP2C76 does not have a corresponding ortholog in humans, and it is **partly responsible for differences in drug metabolism between monkeys and humans**”⁵ (our emphasis).
- Researchers investigated the way that genes affect the metabolism of drugs. It was concluded that the mechanisms involved “differ between humans and cynomolgus monkeys”⁶, in addition “there is little information available on the induction of CYP enzymes in cynomolgus monkey hepatocytes”⁶. **In conclusion, the macaque model being used is not fully understood and macaques have drug-metabolising enzymes that are absent in humans.**
- “It has been obvious for some time that there is generally no evolutionary basis behind the particular-metabolizing ability of a particular species. Indeed, among primates, zoologically closely related species exhibit markedly different patterns of metabolism”⁷.
- A detailed investigation of safety testing by the Toxicology Working Group of the UK’s House of Lords Select Committee on Animals in Scientific Procedures concluded: “the formulaic use of two species in safety testing is not a scientifically justifiable practice, but rather an acknowledgement of the problem of species differences in extrapolating the results of animal tests to predict effects in humans”, and, “the reliability and relevance of all existing animal tests should be reviewed as a matter of urgency”⁸.
- Drs Palfreyman, Charles and Blander in ‘Drug Discovery World’ observed: “One of the major challenges facing the drug discovery community is the poor predictability of animal-based strategies . . . many drugs have failed in later stages of development because the animal data were poor predictors of efficacy in the human subject . . . One of the overriding interests of the pharmaceutical and biotechnologies industry is to create alternative development strategies that are less reliant on poor animal predictor models of human disease . . .”⁹.

Advanced Techniques to Replace use of Primates

Advanced scientific techniques to replace the use of living animals are at the forefront of science. Developments in science and technology have produced systems to study disease and the effects of drugs and other products at the cellular and molecular level. There is a wide range of techniques that can be employed to replace the use of primates, and some of these are described at the end of this report.

Time for change

Although industry and regulators are inherently resistant to changes in the established system, the reality is that animal testing is a poor predictor of human reactions (see section on species differences), and there are alternatives available.

The continued use of non-human primates is not acceptable just because the industry is used to the system.



Cages of monkeys in the HLS experimentation laboratory.

Replacement of primate use with advanced techniques, or other sources of the information being sought, is good for European science and industry, as well as for primates.

There must be a drive to replace primate use in regulatory testing – primates are a comparatively small part of the regulatory testing strategy for new products, used at a late stage, after tests have been conducted on other species. The use of primates in regulatory testing could, therefore, be replaced more easily than was the case for the EU cosmetics testing ban for example, which was more complex because it needed a ‘start to finish’ replacement strategy.

If the European Parliament and Member States are to respond to public concern and take serious steps on this issue, then it is vital that the animal tests be ended earlier in the regulatory testing programme and advanced non-animal techniques such as microdosing and toxicogenomics are used to replace animals.

The fact that primates come late in the testing strategy means that by the time the monkeys were being strapped into restraint chairs for the experiments we have described below, hundreds even thousands, of smaller animals would already have died to test the same product.

The Investigation

This study of the use of primates in regulatory testing includes an insight into the functioning of a typical European commercial testing laboratory. An ADI/NAVS investigator worked as an animal technician in the primate toxicology units at Huntingdon Life Sciences (HLS), Cambridgeshire, UK for a year, until the summer of 2008. Duties included cleaning and feeding the animals, as well as observing and assisting researchers and senior technicians with procedures; training included a UK Home Office animal technician training course.

HLS is a commercial toxicological testing facility. The nature of the experiments it conducts on behalf of its clients is to look for adverse effects or symptoms of test compounds. Its clients are manufacturers of drugs, chemicals and other products. They include GlaxoSmithKline, the Ministry of Defence, AstraZeneca among others.

HLS has two establishments in the UK at Huntingdon Cambridgeshire and Eye, Suffolk, with its headquarters in the USA and the company employs in the region of 1,700 people. All of the experiments discussed here took place in the primate units in the HLS Huntingdon laboratories, which employs in the region of 900 people.

Suppliers and Travel

During the period of our study, the company held 25 Home Office licences carrying a 'mild' suffering protocol, 148 with a moderate suffering protocol, 36 substantial suffering and 3 unclassified²⁰.

This is therefore a major contract testing operation providing testing facilities to wealthy multi-national manufacturers of a range of products. HLS offers its clients: dogs, monkeys, mini-pigs, rodents, guinea pigs and rabbits; it also has capacity for larger animals, such as horses. The beagle block holds up to 2,500 dogs at any one time²¹.

There were many studies (animal tests) under way during the time that the investigator worked in the primate units. The units had capacity for 550 monkeys at any one time, and the numbers of monkeys used in the tests observed during this investigation ranged from 4 to 72. Just five studies accounted for the lives of 217 monkeys.

The number of primates killed each day depended upon the status of the individual study and the capacity of the necropsy teams to cut up and analyse each animal – each necropsy team could not handle more than 8 animals per day²¹. The investigator commented: *"on the day of the necropsies, the monkeys are silent"*²¹.

Commercial and regulatory tests such as these are not generally published in scientific journals, making critical review of the procedures, the justification and discussion of alternatives difficult. This investigation provides a unique insight into the world of commercial animal experimentation.

Secrecy, accountability

Progress on the development and adoption of non-animal replacement techniques has been slow; regulators are used to the data they receive from animal tests, and the law does not have a mechanism to enable a wider critical review of toxicology tests on animals and input from experts on non-animal methodology.

Any new legislation on animal experiments needs to include a framework and a mechanism to ensure that animal tests are replaced by non-animal alternatives. There needs to be a wider scientific and public scrutiny, **before a licence to use animals is granted**.

An important bar to wider input in the UK is that the government has retained the secrecy clause (Section 24) of the ASPA, and made an exemption from the full provisions of the Freedom of Information Act 2000. A House of Lords Select Committee and the government's own advisory body had agreed with us that there needed to be more openness and accountability on this issue, and that the freedom of information rules should apply. However, although the government accepted this point, it decided to retain the blanket of secrecy that gives rise so much public concern²².

It will be important for European legislation to ensure that assessments of the need for animal use are made with the widest possible scientific and ethical input, before authorisation to use animals is given.

A huge gap in transparency and public accountability exists at the heart of the UK's ASPA (EU Directive 86/609/EEC). This was highlighted in 2005 when the Home Office was questioned about regulatory animal testing at Inveresk laboratories in Scotland. NAVS and ADI submitted freedom of information requests on a number of studies (including primates), only to be informed that the information was not kept.

The reason given was that **authorisations for groups of drugs or chemicals** (i.e., covering many animal tests for individual products within a group of chemicals or pharmaceuticals) – no individual assessment of studies takes place and records of outcomes are not kept. The individual study reports are the property of the client, and the Home Office does not hold copies²³.

In effect, commercial testing laboratories are policing themselves.

Suppliers and Travel

Source of the HLS monkeys

Our investigator understood that HLS itself does not hold a Certificate of Designation to supply animals, but uses a company based on its premises, Belgrave Services, to import monkeys²¹. We were unable to find any record of this company with the Registrar of Companies, although it is cited on a US import document. Belgrave operates one of the buildings on the site, J06, where new deliveries of monkeys arrive. The Head of Department stated that Belgrave Services supplied other laboratories in Spain²⁴ as well as Inveresk Research, in Scotland. HLS Chief Executive Brian Cass referred to the building as a *"stock colony"*, and expressed the hope that HLS would expand its primate use by 80%, whilst actively looking for new suppliers²⁵.

The Head of Primate Toxicology informed the investigator that HLS monkeys arrived from Vietnam, China, and



Nafovanny, Vietnam: Alone in a small metal box.
Next stop Europe?

Mauritius²⁶. During the period of the investigation, the monkeys were supplied by Nafovanny in Vietnam via Belgrave Services²⁷. This included at least eight deliveries of monkeys that were, on average, two years of age (therefore juveniles):

- 12.06.07 – 56 Monkeys
- 31.07.07 – 60 Monkeys
- 21.08.07 – 60 Monkeys
- 18.12.07 – 60 Monkeys
- 15.01.08 – 60 Monkeys
- 22.01.08 – 60 Monkeys
- 11.03.08 – 60 Monkeys
- 20.05.08 – 60 Monkeys

Typically, the monkeys travel by road from Nafovanny in Long Than to Ho Chi Minh City, they are then flown to France where a freight company forwards them by road to HLS in Cambridgeshire. Personnel at HLS understood the journey to take about 30 hours²⁸, which is typical of the journey endured by almost all macaque monkeys being imported into Europe for experimentation. It is clearly a long, arduous journey in extreme confinement, and stressful for the animals. A study of transport of laboratory primates found “Total journey times to the UK are typically around 30 hours and, in some cases, exceed 70 hours”²⁹.

It is known that cynomolgus macaques react badly to transport. A review of studies in the journal *Laboratory Animal* noted that the cynomolgus macaque “is the type which most frequently has to undergo transportation, yet it is possibly the macaque species least able to respond satisfactorily to it”³⁰.

Monkeys arrived at HLS after midnight, in individual compartments in rectangular wooden crates with a handle at each end. The individual monkey compartments did not allow the animals to stand upright³¹. On arrival most monkeys were frightened and covered at the back of the box³², they were unloaded and released into gang cages in the J06 stock building (although on at least one occasion they were taken straight into the M12 main testing unit³³). In the following days the animals were caught, weighed, health checked, bled for herpes B virus testing and injected with tuberculin just above the eye³⁴. Unwanted animals would remain in this unit for some months before being euthanised³⁵.

Observations of injuries and illness related to the journey included: high temperature and weight loss³⁶; abrasions to



Nafovanny, Vietnam - a major supplier of primates to European laboratories. Row upon row of rusting, dilapidated, tiny cages each containing a solitary monkey - some cages are collapsed, at angles, and with the monkeys living inside.

heads and faces³⁷; the study notes for BVR0963 noted that one monkey arrived with bruising and a swollen orbital³⁸; a monkey in the stock building had skin looking sore and flaking off badly, requiring its feet and tail to be bathed in Malaseb for 10 minutes every other day; it was claimed the animal had arrived in that condition³⁹.

The supplier: Nafovanny, Vietnam

In addition to the arduous journey made by every monkey before it reaches HLS for experimentation, consideration must be given to the matter of how these animals are cared for at the supply source and what welfare standards, if any, can be imposed on a foreign supplier.

HLS falls under the jurisdiction of the Home Office with Designated Establishment Certificates and Project Licences issued in accordance with the Animals (Scientific Procedures) Act 1986 (ASPAs). Belgrave Services, operating from building J06, should hold a certificate of designation as a supplier.

However, the monkey supplier Nafovanny, is outside of Home Office jurisdiction. As the UK's Animal Procedures Committee has noted: "An overseas primate breeding and supplying centre cannot be a 'designated establishment' in the same way as they would in the UK, because they are outside the UK's jurisdiction"⁴⁰. "The inspectorate has no jurisdiction outside the UK, and therefore, where animals are supplied from outside the UK, any site visits by the Inspectorate depends on negotiation and cooperation"⁴¹.

The 2005 report of the Animals (Scientific Procedures) Inspectorate Report (ASPI) states that "before primates can be acquired from an overseas breeding centre it is necessary for the Home Office to have appraised and accepted the use of that centre in order to ensure compliance with the section of the Home Office Code of Practice for the Housing and Care of Animals in designated Breeding and Supplying Establishments (1995 HC 125) pertaining to the import of primates"⁴².

Nafovanny was formed to export macaque monkeys for experiments, as a joint venture between the Vanny Group of Hong Kong and Naforibird Company of Ho Chi Minh, Vietnam⁴³. The monkeys originate from two large facilities in Long Thanh, Vietnam.

In November 2008, we filmed monkeys inside Nafovanny living in deplorable conditions. Some were housed in isolation in small cages under one metre high, little taller than the monkey itself, when standing upright. The bare cages had solid metal sides and backs and metal mesh tops, and stood on short legs, raised off the ground. Several

cages were in a state of collapse – leaning at extreme angles, forwards, backwards or to one side – with monkeys living inside them. Several hundred monkeys were in these cages, spanning the rear of the main site in Long Thanh. Other units we observed provided group housing, but were small and lacked enrichment.

In 2005, the UK Home Office stated: *“In effect we will only allow the use of animals from overseas centres we believe produce purpose-bred animals to acceptable welfare standards”*, and in March that year the ASPI visited the Nafovanny facility in Long Thanh⁴⁴. The visit identified *“shortcomings in animal accommodation and care”*, and the centre was notified that, *“its status as an approved centre would cease”* once all existing orders for primates had been filled. By the end of 2005, however, the Home Office had received *“reassurances and evidence that significant improvements had been made”*. This led the Home Office to believe that Nafovanny should, in future, be able to meet the expected standards, but they issues the caveat that if the centre wished to supply more animals to the UK *“we will visit the relevant facilities”*⁴⁵. The Home Office later stated that this evidence came in the form of *“unedited video footage, photographs and reports”*⁴⁶. In 2007, it was confirmed that the site had not been visited since March 2005⁴⁷.

Our footage from November 2008 indicates that the Home Office is unable to raise the standards of foreign suppliers to an acceptable level.

It is extremely difficult for governments to control standards of welfare for the thousands of monkeys that pour into European laboratories each year. Any government assertions that foreign suppliers will not receive designated supplier status unless they can meet modern scientific and welfare standards, are really more of a public relations exercise than measures of control.

The primate environment and animal welfare at Huntingdon Life Sciences

Husbandry

The primates used at HLS Huntingdon during this investigation were cynomolgus macaques (also known as crab eating macaques)⁴⁸. These are the most commonly used monkeys in commercial testing in Europe. The laboratory has a capacity for 550 monkeys but hopes to increase this to 700 or more^{26,49}. On arrival the monkeys are placed in unit J06, operated by Belgrave Services, although HLS staff were also employed in this unit. The monkeys would then be moved to the HLS unit M12 for experimentation⁵⁰.

Unit J06

Referred to by Chief Executive Brian Cass as the “stock colony”, animals arrived here from Vietnam⁵¹. There are 14 gang cages with a capacity for 15 monkeys each, providing a capacity for up to 210 animals^{50,52}.

A wide walkway runs down the centre of the room with small ‘catching’ cages on either side. Approximately, 2.13m high x 1.22m wide, these are constructed from metal bars with solid dividers between each cage, and a small sliding door through which monkeys can be removed⁵².

Behind each catching cage, connected by a small, closable port, are slightly larger gang cages housing up to 15 monkeys. These have shelves for perching, and limited toys had been provided⁵².

To catch animals, a worker enters the cage and chases the animals into the catching cage⁵².

Unit M12

This is the main primate testing building with a range of different caging:

Teversham Type: Approximately 1.22m x 0.91m x 0.91m with a single horizontal perch. Side and rear are solid and the rear wall can be pulled forward to crush the monkey to the front bars. The cages are stacked two high. The sides can be removed so that the monkeys have access to the next cage and usually live in groups of three²¹.

ArrowMight Type: These cages are integrated into the room, on either side of a walkway. A maximum of four monkeys live in a cage with a tarmac-like floor divided into two sections; a tall cage approx. 2.44m x 1.22m with a shelf to perch and a door for laboratory personnel; the second section includes a metal back that can be pulled forward to crush the monkeys to the front for capture²¹.



Stock colony J06: This is where monkeys arriving from Vietnam are housed. In terms of space, companionship and enrichment this is the best the monkeys get. No natural light or vegetation and limited, basic climbing frames. The gulf between how welfare is perceived inside and outside of the animal research community is apparent. Twenty years of regulation has failed to provide welfare that matches public assurances. These conditions would be distressing in an impoverished, unregulated zoo, yet this is a company with annual profits of €37million.

Gang Type: A walkway runs down the centre of the unit with cages on either side formed by thick metal bars running from floor to ceiling. This has a tarmac floor and allows the monkeys to live together. There are a small number of pipes, bamboo poles and toys in the cage for the monkeys to play with ²¹.

Husbandry-related welfare issues

In the wild, cynomolgus macaques live mainly in trees, in large troops of 50-100 animals, with an average home range of almost a kilometre. The family group can wander over a distance of up to 1.5km per day⁵³.

These monkeys have shown intelligence and emotion in the laboratory. One paper described, *“Following treatment he would cry if placed in his cage immediately, because he wanted to spend a little more time outside being held or groomed by the attending technician”*⁵⁴. This monkey was therefore aware of his actions and was able to moderate his behaviour in order to affect the behaviour of other animals – in this case his human carer. The animal is therefore aware of how his behaviour can evoke a specific behaviour in other animals – not just those of his own species.

Recently, it has been noted that cynomolgus macaques have carried out successful fishing behaviour, which others in the group observed and attempted to copy⁵⁵, thus demonstrating intelligence, sentience, and components of a culture.

The investigator’s descriptions and photographs show the group enclosures to be barren and uninteresting²¹, whereas guidelines for the care of captive primates recommend that enclosures *“should ordinarily allow the animal to adopt as wide a behavioural repertoire as possible, provide it with a sense of security, and a suitably complex environment to allow the animal to run, walk, climb, jump, and sleep comfortably. Materials providing tactile stimuli are also valuable”*⁵⁶. Clearly the facilities at HLS are small, impoverished in terms of enrichment, have no natural light, have a substrate of metal or a hard tarmac-like surface and would be unlikely to be acceptable in any modern zoo.

No objects of real enrichment value were provided to the monkeys to engage their interest, stimulate thinking and manipulate, operate or investigate (e.g. puzzle feeders). Where some enrichment was added to the cages it was of poor quality and included plastic dumbbells, nylabones/rings, mirrors and metal triangles. The monkeys were given one toy between 8 animals³², so invariably, these were monopolised by the more dominant animals. The investigator had been told that puzzle feeders were “too expensive”⁵⁷.

HLS should be aware of expert advice on the keeping of laboratory monkeys, for example, *“It may be necessary to provide a number of devices to group-housed animals so that more animals have access”*⁵⁸. And, *“The variety of effective feeding enrichment options for captive primates is impressive and an incentive to provide all animals with means to express their drive to gather and process food”*⁵⁹.

A study of stress in captive macaques found *“A husbandry practice as simple as dispersal of food can profoundly affect both behavioural and physiological responses in macaques”*⁶⁰. However at HLS, the monkeys were either fed by food hopper, or food was simply scattered on the floors of the cages.

It would therefore be difficult to describe the HLS primate facilities as anything more than the bare minimum. This is a wealthy company providing these highly intelligent animals with just enough to sustain them before they are experimented upon. As a result, negative impacts on the animals arose from the nature of the housing:

A monkey in a unit where a diabetes drug was being tested was discovered with blood on its face, on the back of the cage and the ends of the animal’s toes were missing. Some staff suggested that the monkey had chewed off its own toes, however the investigator noted that the wounds were clean straight cuts and concluded that the animal was more likely to have trapped its foot in some part of the cage and sliced them off trying to free itself, and then put its foot in its mouth. Missing digits were not considered to be an uncommon occurrence⁶¹.

Such injuries indicate that the monkeys had access to sharp metal edges when they reached through their cages, which is extremely poor management and design. Again, HLS is in the position to benefit from advice provided in standard texts on working with primates ***“cage design should minimise the risk of skin penetration, whether from sharp metal, rough surfaces, a fingernail or a bite. They should be made without sharp edges internally or externally”***⁶².

A male monkey on the Humab study cut his hand open; this was glued by the vet, but became unglued 10 minutes later⁶³. A female cut her arm, possibly on the food hopper. The vet cleaned the wound and applied two staples, which she removed on returning to her cage; she was re-caught, her injury was glued shut and she was given an anti-inflammatory ⁶⁴.

The high level of handling that the monkeys must endure in a laboratory environment also increases the risk of injury from caging. At HLS monkeys would get scrapes whilst being removed from their cages and animals were also seen

Health and sickness

running into the glass doors at the ends of the units⁶⁵. One monkey caught his head on the cage whilst being removed and it required 8 staples to close the wound⁶⁶.

Training the animals with rewards would reduce escape attempts and therefore injuries; it would make handling less stressful for both animals and staff. It has been recommended that “On both welfare and scientific grounds efforts should always be made to train the animals to accept handling and so avoid capture/restraint and/or sedation”⁶⁷.

Monkeys are dextrous, intelligent and will make efforts to escape the inhospitable laboratory environment. Two females escaped during the Humab tests (see Humab study, later), because their cage was not properly secured. One got into a cage with 3 large males and was attacked and possibly raped. Her face was bruised and battered, a finger was bitten, her genital area was scratched and bruised and her anus was ripped and covered in mucus. She was given antibacterials, painkillers and emergency contraception⁶⁸. Less than four months later, two males and two females, from the same test escaped their cages overnight. The animals had broken their own cage doors open⁶⁹. The second incident would indicate that security was either not increased, or if measures were taken, they were inadequate.

Whilst being removed from a cage for bleeding during the HIV vaccine study, a female monkey escaped and ran across the fronts of the cages; three males in one cage grabbed her and she was bitten⁷⁰.

Three males and a female on the HIV study escaped by breaking the locks on their cages. They were discovered on a Sunday morning, with the female hiding under the cages. The customer was informed and requested that chains be placed around all the female monkeys' doors⁷¹. However, the chains holding a cage door shut had sharp edges and one pierced the cheek of a female monkey, leaving her unable to eat; as a result she was force-fed twice a day. She was treated with an antibiotic and an anti-inflammatory⁷². It should have been possible to secure these sharp ends away from the animals, especially since a similar incident had occurred a few weeks earlier, with another monkey⁷³.

Prevention of such injuries should be top priority for companies such as HLS and its clients (for example GlaxoSmithKline profits for 2007, after taxation, were £5,310 million⁷⁴). Broken doors, rough-edged chains and substandard facilities are inexcusable.

Health and sickness

In study **BVR1013**, one monkey displayed aggression towards the others and so was housed alone. When this animal was taken out the cage to be dosed by oral gavage, he vomited faeces, which he'd apparently eaten in his cage. He then had a nose bleed. After one dosing session a technician pointed out that the monkey had laid down and recovered after a few minutes^{75,76}. As recovery was rapid after being returned to his cage, it is possible that all the clinical signs were a result of stress rather than an effect of the test compound.

It has been established that the consumption of faeces can arise from food deficiency, boredom, social stress and medical problems in captive primates⁷⁷, and as single housing can cause increased suffering, a more flexible approach should have been taken to his management, as described by Wolfensohn and Honess (2005)⁷⁸. Despite the fact that clinical signs such as this would be important to the study, it was later noted that the events concerning this monkey had not in fact been recorded⁷⁹. Two weeks later, this poor monkey was still being used in the study while it continued to suffer nose bleeds and vomit faeces⁸⁰.

During their time at HLS, a few animals in the stock group for study **VKS0527** were noted to be suffering constant diarrhoea from the time they were transferred to the unit^{81, 82}, some were also vomiting^{83, 84} and one continued to salivate for two hours after oral dosing⁸⁵. One monkey on this study suffered a chronic skin condition which did not clear up, despite numerous treatments⁸⁶⁻⁹⁰. One unfortunate animal also died suddenly after being dosed⁹¹.

Animal 205050548: This particular animal suffered from continual and sustained ill health and is an example of the extent of suffering endured by some individuals in establishments such as this. The animal arrived from J06 with sunken eyes⁹²⁻⁹⁷ and around a week later the vet was called because the monkey had suffered from persistent diarrhoea over several days. The vet gave anti diarrhoeal and rehydration drugs⁹⁸. During the following weeks the animal's condition did not improve, despite further drug treatment⁹⁹, and blood was seen in the faeces¹⁰⁰. A vet took a faecal sample and found the animal had a gut parasite. The animal was finally treated for this condition¹⁰¹. On the next examination the animal was found to have no gut parasite in her faeces, but was still suffering from diarrhoea, particularly when stressed during removal from her cage. The vet re-examined her and suggested that the animal was suffering from a permanent inflammatory stress condition¹⁰². The monkey was diagnosed with further gut parasites around three weeks later and was placed on another treatment regime¹⁰³⁻¹⁰⁸. A further five weeks later the animal was again treated with antibiotic subcutaneously; the investigator noted “*someone says she has campylobacter*” (another



The tragic reality is that this is an industry that simply cannot provide for the needs of primates and that is why these experiments must stop.



Rows of monkey cages inside experimental unit M16.

Procedures, handling and restraint

gut infection)¹⁰⁹. The investigator wrote, “*none of the treatment ever truly cured her. On the day I left she still was showing signs of diarrhoea. She will stay there and be transferred to a project licence that allows her to be used simply for providing blood. She will remain as a stock animal, already having been separated from the original monkey that she shared her cage with on arrival and now currently lives with number 852...She will probably spend the rest of her life just sitting in her cage with her cage mate, having no other interaction than when she is bled every so often*”¹¹⁰.

A female on the **HIV vaccine study** was found to be lame with a swollen knee, and it was understood that the vet prescribed painkillers and anti-inflammatories¹¹¹. A week later she showed “*severe muscle wastage on its leg during health check due to not using it*”^{112, 113}. Two weeks later she was killed at the end of the test. During the necropsy, it was discovered that she had suffered a torn ligament¹¹⁴.

Procedures, handling and restraint

Most procedures carried out on primates at HLS require restraint. Capturing monkeys from their cages involves a technician placing a gloved hand in the animal's cage and waiting until it either moves to the front of the cage or attacks the gloved hand, at which point the monkey is grabbed. Three workers are needed; two to hold the animal, one to perform the procedure. This allows routine procedures such as blood sampling, dosing of product under skin or into muscles, oral dosing (gavage dosing), temperature recording and tattooing. The monkey's arms, legs and tail will be held and the animal may be held face up or face down. For inhalation dosing and blood pressure recording, animals are strapped into restraint chairs.

Two animals in study **JLY0120** were not dosed as one of them suffered repeated prolapses and was to be replaced¹¹⁵. Three monkeys suffered rectal prolapses during an incontinence drug study¹¹⁶. Rectal prolapse is known to be indicative of gross stress in restrained non-human primates¹¹⁷.

In addition to being distressing for the animal, handling and restraint is where there are likely to be problems in the human monkey interaction. For example, a member of staff was bitten whilst catching a monkey on the **diabetes drug test**; as the animal was biting him, he grabbed its head and twisted it (he was subsequently moved to another unit)¹¹⁸. Aggression from workers caused by mishandling and fear in the animals, highlights the need for a higher level of supervision and training of staff working with primates¹¹⁷.

It is clear that HLS management needs to invest more money, time and effort to increase supervision, improve facilities and implement a training programme for the staff and animals – it is recommended that, “*Well-trained, competent and motivated personnel can make an enormous difference in improving the welfare of captive primates. The institution should ensure that people caring for and using primates are properly trained and exercise high standards of humane care and treatment*”⁵⁶.

Reducing stress and suffering during routine procedures

Others working with primates elsewhere, have devised ways of reducing stress and unnatural physical contact the animals are forced to endure:

Oral dosing

Oral dosing (gavage dosing), involves forcing a rubber tube down an animal's throat; the test compound is injected or pumped down the tube, into the stomach. Our video shows three people holding a small monkey for this procedure, and it is clearly afraid and in great distress¹¹⁹. One is holding the arms, another the legs, and a third worker is feeding the tube down the animal's throat. Yet instead of this, HLS could use a dough type feed into which the compound has been inserted. A recent study reported “*Because consumption is voluntary, it is entirely stress free, unlike gavaging...In all cases, the purpose of the study was achieved, even during pharmacokinetic studies where immediate ingestion of the material is critical*”²⁰.

Blood sampling

Blood sampling can also be made less stressful through training. “*It takes a cumulative total of about 1 hr to train an adult female or adult male rhesus macaque successfully to present a leg voluntarily and accept venipuncture in the home cage*”²¹.

Studies of welfare and best practice in management of primate facilities, have recommended “*facility managers and principal investigators must ensure appropriate staff levels and sufficient time for training before studies begin, and consider how they can best support their staff to work with co-operative, trained animals rather than resisting, fearful, ones*”²².



A monkey is strapped down and experimented upon in front of the other caged monkeys.

Stress from handling and from anticipation of procedures

There is no doubt that monkeys subjected to procedures on a daily basis suffer increased stress and anxiety, which can affect experimental outcomes: *“Studies demonstrate that there are long-term consequences of monkeys’ experiences with experimental protocols, such that they may develop cognitive expectations about procedures that affect the data collected compared with experimentally naive subjects”*⁶⁰.

During the **incontinence drug study**, several animals suffered **rectal prolapses**. On 18.06.07, one animal prolapsed during dosing and a technician attempted to help the animal by trying to re-insert the prolapse with a bottle spout but was unsuccessful, and the veterinary surgeon was called^{123,124}. The level of anxiety that can cause this condition is well known: *“Being removed from the familiar home cage during most restraint situations adds to the anxiety experienced and subjects often show gross signs of distress such as acute diarrhoea, **rectal prolapse** and alarm vocalization”* [our emphasis]¹¹⁷.

For an animal to experience sufficient stress to trigger a rectal prolapse, is a significant event which should be acted upon promptly. Clearly, HLS needed to take action on these incidents. The scientific literature advises a number of behaviours that are used to determine psychological distress, and these include *“an increase in disease processes, e.g. diarrhoea and rectal prolapse”*²⁵.

Others have noted that stress in laboratory animals can affect experimental outcomes, and this can arise from anticipation of procedures, too: *“Stress responses in the animal result in the release of hormones and other substances to counteract the stress, which can cause anomalous experimental results”*²⁶, and, *“the expectations of these animals anticipating daily capture, manhandling and dosing can also impact on test data”*⁶⁰.

Even events which staff may consider routine can be a source of stress to the monkeys, *“stressful housing conditions, loud noises, restraint, sensory deprivation, and separation from companions function similarly to electric shock to hamper the antibody response to bacterial and viral infections and possibly to worsen parasitic infestations”*²⁷.

Expert advice is that it is important to consider that each animal being used is an individual being. *“We cannot consider our experimental subjects to be uniform test tubes to which we add our experimental reagents. We must consider the social context, species differences, and individual differences...Failure to do so will result in welfare procedures that do not work and research results that are uninterpretable”*⁶⁰.

Unfortunately, commercial contract testing laboratories like HLS are based upon high throughput rather than assessing



Monkeys severely restrained for an inhalation study. For some the stress was so great that they suffered prolapses. Our DVD *Save the Primates* shows the monkeys' reaction to what was happening to them.

the needs of individuals. The emphasis is, inevitably, on processing large numbers of test compounds, using large numbers of animals. We would submit that this can only lead to poor data.

This makes it all the more vital that scrutiny of project licences for commercial regulatory testing is carefully managed, and that group authorisations are not allowed.

During oral dosing study **SOI/0052**, several animals suffered from vomiting and salivation on numerous occasions¹²⁸⁻¹³⁰. Several monkeys produced black-stained urine on their cage floor¹³¹. One almost chewed off its finger, gnawing into bone, and continued chewing the hand after it had been dressed by the vet. Others were showing symptoms and behaviours such as tugging at chest skin, pushing their fists into their mouths, trying to bite through the metal food hopper, pushing large amounts of sawdust into cheek pouches, chewing metal and dragging teeth along the bars of the cage¹³² and also, five days later, showed signs of twitchy feet, indicating a kind of pins and needles sensation^{133, 134}. Several animals were clearly distressed yet they were orally dosed as normal and returned to their cages.

At around the same time, a study of the same product was started in rats and researchers had noticed the rats chewing their feet and eating sawdust^{132,134}. Almost chewing off a finger is a very significant clinical sign, causing substantial pain, so as a result, the dose for one group was lowered.

Such events illustrate how predictive severity banding (which was not higher than moderate in this case) can often be wrong and that a new system incorporating retrospective review of such studies would better inform future tests as well as improve animal welfare protection.

An inhalation study provided another example of how the **severity of a procedure can be misjudged:**

Over a period of time three monkeys on an inhalation study died or had to be killed due to partially collapsed and blocked lungs. Three other animals also collapsed but were revived. Necropsied animals were found to have blackened lungs¹³⁵⁻¹⁴⁰. Clearly these animals would have suffered a great deal.

Due to the severity of the problems and unexpected deaths an internal meeting was held where licensing implications were discussed¹³⁷, as this study was licensed under a 'mild' severity limit protocol.

Home Office regulations stipulate **"The project licence condition will be regarded as breached if the Home Office is not notified promptly...when a protected animal has... suffered (or is likely to suffer) more than is authorised by the severity limit"**¹⁴¹.

Welfare and suffering related to specific studies

The first animal to suffer a severe effect (death) had died three weeks before the meeting to discuss the implications related to the severity banding of the licence. **Consequently animals continued to suffer significantly beyond the severity banding on the licence, which in our view, represents a breach of the licence conditions.**

It is shocking that the monkeys must have been aware of what was happening around them, as our video shows procedures being performed in front of cages of monkeys¹⁴², and the investigator noted how the monkeys would go silent on the days of the killings and necropsies¹⁴³.

Welfare and suffering related to specific studies

HIV vaccine

This study used 72 monkeys, in 4 groups. Dosing was by mainly by injection into the muscles, and into the vein on one occasion, followed by a range of observational procedures such as regular bleeding, and the animals were killed and sent for necropsy at varying times. This was carried out for 4 days, 14 days or 13 weeks, up to 26 weeks, dependant upon the study¹⁴⁴.

Diabetes drug

This used 4 monkeys. The test compound was administered to each monkey over the course of three months, on three separate occasions, intravenously (into vein), by inhalation and subcutaneously (under the skin). On each occasion, the monkeys were dosed and then bled for 17 days. After this they were given a break before the next dosing. Over the total period, each monkey was bled 84 times. At the end of this study, the four animals were killed, but none were taken for necropsy¹⁴⁵.

Incontinence drug

The test substance was given daily by oral gavage, over a period of 52 weeks. The monkeys were removed from their cages, restrained by two people, and a third pushed a tube down the throat to deliver the product being tested. A “flush” substance is given after the compound¹⁴⁶. Some of the monkeys vomited every time they were dosed¹⁴⁷, particularly the control animals¹⁴⁸.

The fact that both the test and the control monkeys were vomiting indicates that the oral gavage procedure itself, rather than the test substance, was causing the problem. It has been noted elsewhere that, especially with primates, “gavaging is unpleasant for the animals, requires highly skilled staff, and, in the case of unanaesthetized animals, carries a risk of injury to both the animals and the operator”, and, the observation that non-human primates will “forcefully resist such intervention”²⁰.

The investigator became concerned that the animals were being dosed “right on the limit”, reporting, “monkeys are dosed at a volume of 10ml/kg”¹⁴⁶; it is advised that the oral administration volume for rhesus macaques is 10ml/kg¹⁴⁹.

Other laboratories have refined their methods to avoid the use of oral gavage and minimise the stress suffered by the animals (such as the dough-type feed carrying the compound, described earlier), but not it would seem, HLS.

As mentioned earlier (in ‘procedures, restraint, handling’), it is important to bear in mind that these monkeys were undergoing dosing every day for an entire year, so they would anticipate what was about to happen to them. The long-term consequences of these experiences can affect experimental outcomes⁵⁰.

During this year-long study, several animals suffered prolapses, which appear to be the result of fear due to anticipation of the procedures (see earlier: Procedures, restraint, handling).

The overall level of suffering on this study was severe, prolonged and could have been mitigated.

HLS managers need to review their training and procedures, in light of modern thinking, for example “Primates should be trained to co-operate with restraint and handling using positive reinforcement techniques”¹⁵⁰.

HuMab (anti-inflammatory (painkiller) drug

This study involved 36 monkeys; 3 groups given rising doses and one control group. Each group included “recovery animals” who underwent an 8 week recovery period. The animals were dosed once fortnightly, on days 1, 15, 29, 43, 57, 71, 85 and 99. Recovery animals survived until day 155¹⁵¹.

On dosing days the animals were caught, restrained, a needle inserted into either the vein in the back of the leg or in the arm. The dose was injected over a couple of minutes and the animal returned to its cage¹⁵¹.

Welfare and suffering related to specific studies

On 22.09.07, two of the animals on this study were noted to have ophthalmic abnormalities¹⁵². Abnormalities in the eye were one of the conditions being screened for regularly¹⁵¹, therefore it had been anticipated that the animals might undergo ocular changes during the tests. It is possible that an ophthalmic abnormality, of any severity, would be capable of causing distress to the animal concerned. It has been noted that the primate's "*sensory emphasis is visual. Their forward facing eyes and highly developed visual centres in the brain are associated with the three dimensional, stereoscopic, colour vision that primates have*"⁷⁸.

Blood Clotting drug

This protocol involved 56 cynomolgus macaques, in 7 groups. The test substance was administered by intravenous injection in the vein in the back of each monkey's leg using an infusion pump. Groups 1 to 5 were given increasing doses of the test compound, groups 6 and 7 also received a clotting factor¹⁵³.

One week prior to study, all the monkeys were bled; the night before dosing, they were fasted. On the dosing day they were removed from their cages, restrained by two people and a third inserted a cannula into a vein at the back of the leg. The animals were placed in restraint chairs, connected to the pump and the substance infused over 2-15 minutes. Half of the animals were then returned to their cages. At the end of the day they were fasted. The following morning, they were removed from their cages, bled, sedated, killed and sent to necropsy. Blood had been taken from the other animals when the cannula was initially inserted. They then had blood samples taken at 12 points over the next 24 hours. Two weeks after dosing, this second group was fasted overnight, bled, sedated, killed and sent to necropsy¹⁵³.

On 10.09.07 the animals were fasted and bled, but a fault with analysis equipment meant the animals had to be bled again the following day, so they were re-fasted¹⁵⁴. Although a common procedure in laboratories, fasting would have caused some distress, as animals become accustomed to routine meal times.

On 19.09.07, one female was trembling during dosing, indicating distress. It is known that biochemical changes in the body as a result of stress can influence the outcome of a test "*Stress responses in the animal result in the release of hormones and other substances to counteract the stress, which can cause anomalous experimental results*"²⁶. Primates suffer stress when placed in a restraint chair, even when they become used to it, and it is known that they "*show rapid behavioural changes when learning a restraint procedure*"⁵⁵.

This monkey's distress could have been reduced with adequate planning and training; "*techniques that reduce or eliminate adverse effects not only benefit animal welfare but can also enhance the quality of scientific research, since suffering in animals can result in physiological changes which are, at least likely to increase variability in experimental data and, at worst, may even invalidate the research. Staff should be given formal training in these operant conditioning techniques*"⁵⁶.

For the second group, a total of 12 bleeds were taken after the initial dosing¹⁵⁶. It is surprising that over a test of such duration no effort appears to have been made to train the monkeys in order to avoid some restraint and manhandling, and therefore reduce stress for animals and workers, whereas others have advised, "*The initial time investment pays off in a safe handling procedure that no longer requires a second person to control the resisting subject*"²¹.

Replacing regulatory safety testing on primates

There are an increasing number of modern non-animal techniques to study human health and test products. These are generally faster, more accurate and, being based on humans, avoid the potentially disastrous consequences of species differences. Modern science requires precision, down to the molecular level, yet we continue to use primates when we are aware of the significant differences between ourselves and other primates. For example:

- Gout is caused by excess uric acid which is produced in monkeys, apes and humans; but only humans get gout¹⁵⁷.
- Herpes B virus in monkeys may cause lesions on the face, lips, mouth, body. Monkeys can carry the virus without suffering the disease; in humans, the disease is rare but is almost always fatal¹⁵⁸.
- Drs Palfreyman, Charles and Blander in 'Drug Discovery World' observed: "*One of the major challenges facing the drug discovery community is the poor predictability of animal-based strategies . . . many drugs have failed in later stages of development because the animal data were poor predictors of efficacy in the human subject . . . One of the overriding interests of the pharmaceutical and biotechnologies industry is to create alternative development strategies that are less reliant on poor animal predictor models of human disease . . .*"¹⁵⁹.



Modern science: Accelerator Mass Spectrometry offers precise analysis of samples from volunteers who have received micro-doses of test compounds.

- Studies have shown that on average, **effects in humans differ from those in laboratory monkeys a third of the time.** Even if the way drugs break down and are excreted are similar in monkeys and humans, metabolism rates differ radically¹⁶⁰.

The consequences can be either disastrous in terms of human health or missed opportunities, for example:

- An anti-Parkinson's disease drug, tolcapone (Tasmar); withdrawn from the market in 1998 after links to deaths from liver disease¹⁶¹. Similarly, the antidepressant Seroxit was also linked to liver damage, in 1997¹⁶².
- The safety of donepezil for Alzheimer's came under review in 1999 resulting in updating of product information¹⁶³, and clinical trials of a potential Alzheimer's vaccine were suspended when participating patients began experiencing side-effects to the nervous system^{164, 165}. The vaccine had been hailed as *"revolutionary ..following encouraging tests on animals"*¹⁶⁶.
- The therapeutic effects of the appetite suppressant fenfluramine for autism and its potential to reduce suicidal tendencies were discovered in people and could not have been predicted in animal experiments¹⁶⁷.
- The drug chloramphenicol does not have the adverse effect in monkeys and dogs that it has in humans¹⁶⁸.
- The drug azauracil caused no apparent toxic effects in monkeys; in humans, it produced unpleasant effects that caused its use to be stopped¹⁶⁹.

Such differences were grimly illustrated when the UK drug trial for test drug TGN1412 was almost fatal to human volunteers who suffered multiple organ failure caused by an uncontrollable immune reaction. Side effects included: Soaring body temperatures; dilated blood vessels; falling blood pressure; swollen neck and head; limbs turning purple; permanent damage to immune system; fingers and toes requiring amputation; early signs of cancer; early stage lupus¹⁷⁰. The laboratory tests on monkeys gave doses of the drug 500 times that given to the human volunteers, without side effects. Now many agree that this disaster could have been avoided by using microdosing¹⁷⁰, which involves giving ultra-low, safe doses of new compounds to human volunteers and samples of blood or urine can then be analysed by Accelerator Mass Spectrometry (AMS). AMS can show how compounds are absorbed, distributed, metabolised and excreted by the human body¹⁷¹.

Critique of studies observed at HLS

And this is not the only advanced non-animal technique, ready to replace primate use, others include:

- toxicogenomics
- biochips
- advanced scanning techniques
- computer database and analytical programmes - DfW, high throughput screening
- computer modelling
- QSARs (chemical structure-activity relationships)
- studies in human cell, tissue and organ cultures
- 3-D tissue engineering

Critique of the studies observed at HLS

Studies observed at HLS included an HIV vaccine; a diabetes drug; an incontinence drug; an anti-inflammatory (painkiller); and a blood clotting drug. The nature of the procedures and the suffering of the monkeys has been described earlier. Here, we examine the flaws in the scientific rationale behind these tests.

Study of vaccine for HIV positive individuals

72 monkeys were used to investigate the toxicity and bio-distribution of a therapeutic (not preventative) vaccine based on a chimpanzee virus vector [carrier]¹⁷². Although "... most AIDS vaccine researchers are highly sceptical that it will be feasible to manipulate the immune response in infected individuals to significantly improve their health status"¹⁷³.

The rationale for testing in primates at HLS was that the vaccine involves adenoviral vectors, and in the past adenoviruses have triggered Disseminated Intravascular Coagulation (DIC) in humans¹⁷⁴. However, using animal data to determine the safety profiles of Adenoviral (Ad) vectors has proved ineffectual and dangerous. An NIH report on the safety trials of an Ad vector, which resulted in the death of one participant, stated "*Critically, researchers need to examine more thoroughly the validity of animal model systems used for determining pharmacodynamic and toxicity profiles of vectors*"¹⁷⁴.

The legacy of animal research in the field of HIV vaccines with rhesus macaques is one of failure, with researchers noting that despite tests with simian and simian-human immunodeficiency virus (SIV/SHIV) infected primates, only the outcome of long-term human efficacy trials will demonstrate the effects of a prophylactic vaccine on HIV-1 infection¹⁷⁵. Animal models failed in the Merck STEP Ad5 vaccine trial, with the conclusion "...vaccine protection studies that used challenge with a chimeric simian-human immunodeficiency virus (SHIV89.6P) in macaques did not predict the human trial results.... [Ad5] did cause a substantial reduction in viral load and a preservation of CD4T cell counts after infection, findings that were not reproduced in the human trials"¹⁷⁶.

The monkeys in the HLS study were not infected with a virus, but were simply being used to investigate toxicity and bio-distribution of the compound – something that could clearly have been assessed using a raft of alternative human based methods (see replacements, p.30) and researching the already available data.

Study of diabetes drug

Four monkeys were used to investigate the pharmacokinetics (activity, speed, metabolization) of this peptide with possible anti-diabetic properties. Over a period of three months, each monkey was taken from its home cage and bled 84 times. At the end of the study they were simply killed and disposed of without necropsies being performed¹⁴⁵.

The effects and actions of the hormones being studied vary between species "*Receptors for glucagon and physiologic incretins (e.g., GIP) are present on adipocytes in animals, but it is not clear if they are also present on human adipocytes...*"¹⁷⁷. Others have found a clear species difference in the activity of the drug in humans and non-human primates "*In the baboon, blockade of the effect of GLP-1 could only be achieved at...., five times the concentration that we have found to effectively block GLP-1 in humans*"¹⁷⁸.

It is also significant that the drug being tested was just another version of existing diabetes therapies, which have been shown to be successful in human use¹⁷⁹. Adding to a saturated market with a variant on existing therapies underscores the lack of any scientific justification for tests on primates and highlights the failure to properly assess the product using existing data. This would seem a clear candidate for examination by advanced non-animal techniques rather than yet more animal tests. Interestingly, even in fundamental research elsewhere, human pancreas cells are being used to examine the role of GLP-1 – highlighting that there are no shortage of alternatives in this field¹⁸⁰.



Monkeys in cages used to collect urine. Note the barren environment and harsh mesh floor.

Study of incontinence drug

49 monkeys were force-fed (by oral gavage) daily for a year in order to assess the toxicity of an incontinence drug¹⁴⁶. We have discussed earlier, the misleading results from monkey tests, and this incontinence study provides some stark examples:

In 2002 researchers ascertained which neuro-transmitters and receptors in the body are activated to effect bladder relaxation and thus urine storage. They concluded the *"monkey is the only instance of detrusor relaxation being mediated by the β 3- adrenoceptor alone"*, although they admit there may be a tiny contribution from another subtype of adrenoceptor¹⁸¹. A paper discussing the human bladder reports *"stimulation of both β 2- and β 3- adrenoceptors can relax the bladder"*¹⁸². So in the monkey, one type of adrenoceptor is almost solely responsible, in humans two types of receptors are responsible.

Whilst the purpose of the HLS test was to establish toxicity rather than the action of the drug, when there is such a difference between the species, the model must be questioned.

This supports the need for closer scrutiny of commercial regulatory testing.

A 2004 review of the incontinence drug market found *"there are at least 13 other incontinence drugs currently in phase II development or higher in the US, Europe and Japan. Even if only a handful of these agents are eventually approved, the market is set to become extremely competitive"*¹⁸³.

This appears to be another example of a drug candidate simply progressing through standard tests on animals without that process being informed by existing data.

The use of QSARs (Quantitative Structure Activity Relationships) for existing data, for example, and other techniques outlined later, would have provided an approach more relevant to humans.

Humab anti-inflammatory (painkiller) study

36 monkeys were used to investigate the toxicity/action of the test substance *"fully human monoclonal antibodies" known as BTT* which has an anti-inflammatory action which works by a reducing the extravasation of leucocytes by inhibition of vascular adhesion protein 1 (VAP1)¹⁸⁴.

Replacing primates

Researchers elsewhere (including some working for the HLS client that commissioned this test) are using human tissue rather than animal models, which avoids the problem of species differences. *"We have earlier shown that an anti-VAP-1 mAb blocks extravasation of PMNs [polymorphonuclear leukocytes or granulocytes] into inflamed peritoneum in rabbits and in vitro binding of human PMNs to myocardial vessels in frozen sections of human hearts with a reperfusion injury"*¹⁸⁵.

Furthermore, BTT has already undergone some human clinical trials. The first-in-human study with *"Biotie fully human VAP-1 monoclonal antibody BTT-1023"* was recently reported. Two participants, on the highest dose, reported facial flushing, one of these had facial oedema. These *"are not uncommon events in association with intravenous administration of therapeutic protein drugs"*¹⁸⁶.

An indication of how even with human based test data at the fingertips of the companies, products continue to march relentlessly through standard animal tests.

The use of primates in the development of the new generation of 'biologicals' in the drug industry is on the rise¹⁸⁷. It is of some concern that testing biologicals on primates is simply becoming the latest convention rather than something that has been assessed in a rational way. A discussion on the practicality of replacing non-human primates in the preclinical safety testing of monoclonal antibodies concluded that *"It is clear that from a scientific perspective there are some cases in which the use of Old World primates is not appropriate and other approaches should be considered routinely"*¹⁸⁸.

Blood clotting drug study

56 monkeys were used to study *"a recombinant form of Von Willebrand factor [developed by the customer]...derived from a culture"*. The animals were dosed and bled and killed and necropsied after either a day or two weeks¹⁵⁶.

Von Willebrand disease (vWD) is an inherited blood disorder, characterised by a deficiency or defect in the blood component called von Willebrand factor (vWF)¹⁸⁹. The symptoms of vWD include: frequent nose bleeds, bruising easily, heavy menstrual flow and excessive bleeding following surgery, dental work or childbirth¹⁹⁰.

Recombinant vWF (rec vWF) is produced from mammalian cells¹⁹¹, and it has been known since 1999 that *"rec vWF exhibited activities comparable with plasma-derived vWF, such as platelet binding, platelet aggregation, collagen binding and coagulation factor VIII (FVIII) binding"*¹⁹¹.

The justification given for the use of non-human primates in this study was that the compound being investigated contained Tween 80, which can cause sensitivity in dogs. It would appear that this is a concession to problems with the dog as a test subject, rather than a testament to the monkey being a good model. Tween 80 is known to cause adverse effects in some humans¹⁹². In fact, vWD is so rare in primates that a 2002 paper which described type 3 vWD in a rhesus macaque, stated that *"this is the first report of vWD in a non-human primate"*¹⁹³.

It was reported that the aim of this study was development of a recombinant form of von Willebrand Factor. The HLS client says *"The majority of therapeutic clotting factors continue to be processed using blood-derived components. By applying Baxter's proven proprietary blood-free processing technology, we are working to develop a therapeutic option that will eliminate the potential risk of blood-borne pathogen transmission for people with von Willebrand disease"*¹⁹⁴. However, the contention that the new drug is needed due to problems with existing plasma derived vWF is debatable. Wilate®, is a new generation, double virus inactivated vWF / Factor VIII concentrate, which undergoes processes *"aggressive enough to inactivate viruses efficiently, but yet gentle enough to maintain the structural integrity and function of the VWF and FVIII molecules"*¹⁹⁵.

Almost a decade before these tests on monkeys, vWD experiments on pigs, dogs and mice, had led to the conclusion that *"some differences cannot be avoided"* and that *"...one should be cautious about extrapolating the results from animals to humans"*¹⁹⁶.



Modern science: Preparation of human cell cultures in a project developing an in vitro method for examining human neurotoxicity supported by the Lord Dowding Fund for Humane Research.

It is clear that the use of available human data is preferable to animal studies for such a disease. As far back as 2001, a study was conducted to examine the efficacy of a high-purity factor VIII/von Willebrand concentrate for treatment and prevention of bleeding. The study used 81 patients representing all 3 types of vWD and concluded *“the concentrate effectively stopped active bleeding and provided adequate haemostasis for surgical or invasive procedures”*¹⁹⁷.

Advanced scientific techniques to replace the use of primates in regulatory and commercial testing

Developments in science and technology have provided new techniques to replace animals, which provide data relevant to humans.

An intelligent, cross-disciplinary approach is needed, which draws upon the very best in technology.

There is a clear and urgent imperative: by the time primates and dogs have been selected for testing, other animals have already suffered and died for the same products. Replacement of primates is an achievable goal.

Microdosing and Acceleratory Mass Spectrometry (AMS): A ‘microdose’ is defined as less than one hundredth of the proposed pharmacological dose but never exceeding 100 μ g¹⁹⁹. Drug levels from microdosing can be measured in any biological sample such as plasma or urine to determine ADME (absorption, distribution, metabolism and secretion) and pharmacokinetic characteristics of a drug. Analysis uses an Accelerator Mass Spectrometer (AMS)²⁰⁰, which can count individual atoms and has the ability to detect a liquid compound even after just one litre of it has been diluted in the ocean²⁰¹. A recent EU study over a period of 31 months demonstrated the value of microdosing in drug development²⁰², comparing microdosing data to animal tests. For example, rat data for the compound phenobarbital over-predicted the clearance of the drug in humans, and under-predicted the compound’s half-life (measure of drug metabolism). The microdosing data proved more accurate and was **80% predictive of ADME in people**²⁰³.

This demonstrates that microdosing and AMS is significantly more accurate than primate, dog and rodent models. Microdosing could accelerate drug development. Preclinical studies can take 18 months and cost \$3-5 million. Microdosing can reduce the time to 4 to 6 months and the cost to \$0.35m per new molecule²⁰⁴. Other options for

replacement through microdosing strategies include **PET (positron emission tomography)**²⁰⁵ and human volunteers. It has been concluded that microdosing, could improve selection of new compounds and reduce failures²⁰⁶.

QSARs (Quantitative Structure Activity Relationships) computer modelling; correlates a compounds' structure and properties with its activity. QSAR is used in drug design and environmental risk assessment²⁰⁷, it can play a significant role in assessing toxicity and pharmacokinetics and can be used to determine target organ or system doses²⁰⁸.

Derek for windows (DfW) is an expert knowledge base system (a computer program that applies rules), which predicts a chemical's toxicity from its molecular structure²⁰⁹ by applying QSARs and other knowledge rules²⁰⁹.

Human cell lines: An EU project, 'vitrocellomics' aimed to provide "...new, efficient *in vitro* prevalidation models, which will significantly reduce the use of animal experimentation for prediction of human drug metabolism by 60-80%"^{210, 211}. Specialised cell cultures, such as hepatocytes (liver cells), allow researchers to conduct multiple studies on multiple days using hepatocytes from a single donor to assess intra-assay variability and to study multiple endpoints (i.e. transport and metabolism)²¹². A variety of *in vitro* systems have been under development, derived mainly from the liver, kidney and brain²⁰⁸.

Human tissue use: Pharmaceutical companies use liver tissue to provide biological data and safety test compounds; "*animal drug metabolism is very different to human and it may be more appropriate to use human liver tissue early in a new drugs life to establish metabolites that may be toxic to humans*"²¹³.

Scaffolds and 3-Dimensional (3D) cultures can be formed in different tissue, and used as models for pharmaceutical and drug discovery. The scaffold can be made from synthetic or natural materials, with differing scientific advantages²¹⁴. Tissue can be constructed to recreate whole body systems, such as the human artificial immune system, which assesses a substance's interaction with the immune system²¹⁵.

High throughput screening: This technique, involving robotics and sophisticated control software, rapidly analyses compounds for drug discovery, often to generate starting points for drug development²¹⁶.

Biochips: These show the effect on different cells in the body and how toxicity is altered when the compound is broken down (metabolized) in the human body. They provide "*comprehensive toxicity data very quickly and cheaply*" and can provide data on the toxicity on different human organs²¹⁷.

Toxicogenomics: This seeks to translate data about genetic variation and gene expression into an understanding of the biological systems in organisms, including humans, and the effects of changes in the systems on the organism's health. Toxicogenomics may improve understanding in processes such as reproductive toxicity and nongenotoxic carcinogenesis, usually carried out in long-term animal studies, and "help treat people at the greatest risk of diseases caused by environmental pollutants or toxicants"²¹⁸. Antidote Europe has developed a novel approach to toxicogenomics by using miniaturized DNA chips, in combination with sequential exposure of two different cell types, approximating what would occur in a whole body and call the approach 'Scientific Toxicology Program' (STP)²¹⁹.



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