EUROPEAN COALITION TO END ANIMAL EXPERIMENTS

testing TIMES

Monthly Update on Animal Experimentation Issues in the EU from the ECEAE

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Welcome to the May edition of Testing Times.

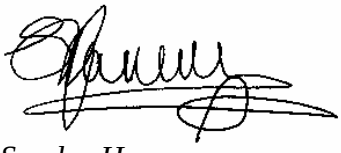
Since the last Testing Times, we have had a highly successful bi-annual Coalition meeting which took place in Vienna in March, bringing together members from all over Europe.

At the meeting we discussed the key legislation that will be coming up over the next year, primarily the proposed revision of the Laboratory Animal Welfare Directive (86/609) and the next stage of REACH. However, there is also the Seventh Framework Programme for Research and Development, Plant Protection Products, the nanotechnology action plan and more to keep us busy.

In this issue, as well as our normal updates, our Scientific Co-ordinator, Dr. Katy Taylor, gives a clear, simple introduction to microdosing and its potential to replace animals used in experimentation.

I hope you enjoy it and please feel free to contact us with any questions or concerns you may have regarding the Coalition or animal experimentation issues.

Warm regards,



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This Issue

Seventh Framework Programme for Research and Development

The European Parliament's Committee on Industry, Research and Energy (ITRE) voted on May 15th on the Seventh Framework Programme for Research and Development (FP7) proposal. ITRE is the lead committee under Rapporteur Jerzy Buzek (EPP/ED – PL). This vote will determine the EU's research and development budget and priorities for the period 2007 to 2013.

In the Environment Committee in February, four key amendments relating to animal experimentation were passed. These amendments stressed the necessity of increasing funding for alternatives to the use of animals in laboratory experiments and the need for the replacement of non-human primates in experiments.

The European Parliament plenary vote will probably take place in June. Given the need for significant funding to develop and validate non-animal test methods and the clear benefits that this

research can bring, it is vital this funding is secured for the next seven years.

Non-Animal Replacement for Shellfish Toxin Test

In March the European Commission validated an alternative non-animal method of testing for the presence of Paralytic Shellfish Poisons (PSP), called the Lawrence Method. This method will now be the default (reference) way of testing for PSP toxins. This is welcome and long overdue (New Zealand has been using a non-animal test for years) and should spell the end of the mouse test immediately. However, the Commission are indicating that this may not be until July 2007, for reasons which are not clear (we have written to them). In addition, as the draft legislation stands, companies would still be able to use the mouse test, which is clearly contrary to Directive 86/609, covering animal experiments generally[1].

Given the substantial suffering involved in the test (it is the equivalent of injecting 3 litres of vinegar into the abdomen of a 60kg person), it is imperative that the mouse test is banned immediately for the PSP toxin.

The Commission indicates that another Shellfish Toxin test, for Diarrhetic Shellfish Poison (DSP), should have a validated alternative by the end of 2006. It is necessary to ensure that a similar delay in implementation will not occur here.

Impact Assessment Begins on the Proposed Revision of 86/609

An impact assessment on the Revision of Directive 86/609/EEC on the protection of Animals used for Experimental and other Scientific purposes began in January and is due to be finalised in October 2006. As a stakeholder, the ECEAE took part in an impact questionnaire in support of the preliminary Impact Assessment.

The present directive does not include ethical review processes or compulsory authorisation of experiments,

Since 1986 worrying new scientific trends have arisen, such as the extensive use of transgenic animals, xenotransplantation and cloning. These require regulation and an urgent review, which the current Directive does not provide for.

Primates are often kept in barren cages with no attempt to enrich their environment

As has been shown by undercover video obtained by one of our members (viewable here), it is apparent that the Directive needs to be revised in order to ensure improvements in the welfare and use of laboratory animals.

Given the slow pace and lack of investment in alternatives methods, there is also a clear need to encourage their development, a need recognised by the Commission.

Finally, the protocol on protection and welfare of animals, annexed to the Treaty of Amsterdam (1997), for the first time committed a legal obligation on European Union institutions to regard

[1] Article 7.2 of Council Directive 86/609/EEC: "*an experiment shall not be performed if another scientifically satisfactory method of obtaining the result sought, not entailing the use of the animal, is reasonably and practically available*".

animal welfare principles when legislating etc and acknowledged that animals were sentient beings.

The European Coalition to End Animal Experiments does not want the regulation of animal experiments but their abolition. However, if they are to take place for the time being, they need to be tightly controlled in a meaningful and effective way, which clearly does not happen at present.

Our four primary demands of the revised directive are:

1. A complete ban on the use of non-human primates in research and testing.

2. An extension of the scope of the directive to include all animals, for example including embryos and cephalopods (such as octopi).

3. A targeted replacement of animals in different types of testing, including an end to:

- xenotransplantation
- the use of animals for military research
- the use of animals for psychological research
- the dissection and the use of animal experiments for education
- the use of experiments involving animals for tobacco and alcohol related experiments.

4. Ending duplicate animal testing through the use of easily accessible databases, freedom of information, enhanced transparency, and a requirement to publish negative results

The Commission proposal is due out at the end of this year or the beginning of the next.

Plant Protection Products: Commission Proposal

The European Commission intends to revise Directive 91/414/EEC on the placing of Plant Protection Products (PPPs or pesticides) on the market and is due to put forward its proposal in June. An impact assessment has been carried out by Civic Consulting and they are due to make public the final report at the same time.

Federation of Young European Greens call for End to Animal Tests

On April 28th, the Federation of Young European Greens (FYEG) called for an end to testing on animals.

Joke Van de Putte, EU affairs coordinator of FYEG, stated, "Instead of testing and killing more and more animals, alternative methods for testing medications have to be developed and implemented. Animal testing for cosmetics cannot be accepted and medicinal testing must be phased out. We appeal to everybody only to buy cosmetic products which were produced without animal testing!"

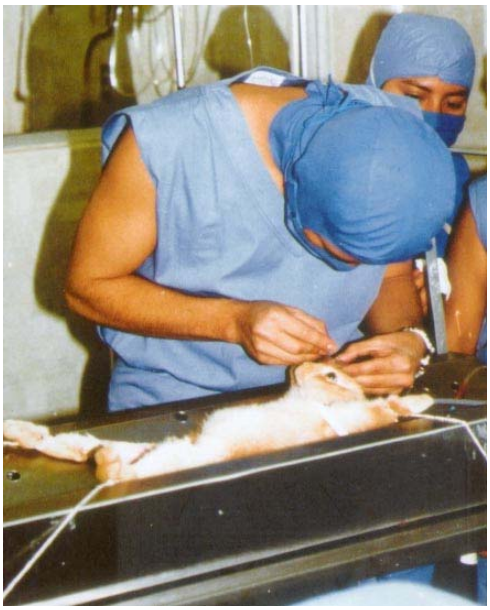
Microdosing – A Short Introduction

What is Microdosing?

Microdosing is a term given to a relatively new technique which involves giving very tiny doses of a chemical compound to human volunteers in order to monitor its pharmacokinetic/bioavailability (PK/BA) profile in the body. The PK/BA profile of a compound describes how it is absorbed, distributed, metabolized and excreted by the body (i.e. its ADME properties). This is an important feature to understand, since a potentially therapeutic drug may be metabolized by the body and rendered either inactive or toxic. It is also of interest to know where in the body these compounds may be distributed, including tissues of particular interest (i.e. the brain, etc.) and how quickly they are eliminated or accumulated. At present, microdosing has only been applied within drug studies but in theory could also be used to assess the PK/BA of any compound. For example, it is also relevant when looking at the effects of potentially toxic chemicals, since due to their PK/BA profile they may be metabolized into something harmless (or more toxic) and/or accumulate in the body.

How does it work?

A microdose is so small that it is not intended to produce any pharmacologic effect when administered to humans and therefore is also unlikely to cause an adverse reaction. For practical purposes this dose is defined as 1/100th of that anticipated to produce a pharmacological effect, or 100 micrograms, whichever is the smaller[2]. It is assumed that the processes controlling the pharmacokinetic profile of a compound are independent of dose level, so a microdose will provide sufficient information to help decide whether it is worth continuing with its development.



Most experiments on animals are performed with no anaesthetic.

The ability to use microdoses has only become a reality with the development of highly sensitive analytical methods such as accelerator mass spectrometry (AMS). AMS can detect very small particles (even atoms) in liquids by measuring their deflection within a magnetic field created inside a specially designed machine. The technique relies on the compounds of interest being labelled radioactively, as occurs with carbon dating. The radio-active label (often ^{14}C) is added in such tiny quantities that it is safe. The compound is administered to the patient (injection, pill form, etc.) and then at specific times, their blood or urine is sampled[3]. This is then analyzed using AMS to detect the amount of the labelled compound in the sample. From this the researchers can work out how quickly the compound is travelling round the body and being metabolised, etc.

For drugs intended to act on the central nervous system, positron emission tomography (PET) can also be used to visualize where and how much of the drug reaches potential targets areas in the brain[4]. This can enable researchers to assess the ability of a labelled compound to reach its target site, such as a receptor in the brain or a tumour[5,6] and to predict optimal doses for clinical trials.

How can it help reduce animals?

Techniques such as microdosing, used in association with technology such as AMS, functional magnetic resonance imaging (fMRI) and PET, provide important data on how novel drugs are handled by the human body, without the difficulties which arise from species differences. In this respect it can be seen to be an improvement on standard method for assessing PK/BA data, which is to use larger quantities of the compound on other species, often rodents and dogs[7]. Since poor PK/BA properties are estimated to account for 40% of failures in the early stages of drug development, it makes sense to have the most accurate information on this *for humans* before costly development continues[2].

Microdosing therefore has the potential to significantly reduce the numbers of animals used in drug and chemical safety studies in a number of

[2] European Medicines Agency (2004) Position paper on non-clinical safety studies to support clinical trials with a single microdose. CPMP/SWP/2599/02/Rev1. See http://www.emea.eu.int/pdfs/human/swp/259902en.pdf

[3] Wilding, I.R. and Bell, J.A. 2005. Improved early clinical development through human microdosing studies. Drug Discovery Today 10 (13), 890-894.
[4] Grasby, P. (1998) psychiatric illness: a PET subject. MRC news 77; 28-32.
[5] Lappin G & Garner RC (2003) Big physics, small doses - the use of AMS and PET in human microdosing of development drugs. Nature Reviews (Drug Discovery) 2, 233-240.
[6] Garner RC (2005) Less is more: the human microdosing concept. Drug Discovery Today 10 (7), 449-451.
[7] Home Office (2005) Statistics of Scientific Procedures on Living Animals, Great Britain, 2004. The Stationery Office.

ways[2,8,9]. Firstly, fewer animals may be required to assess the safety of the chemical *before* it is used in human microdosing studies, since the amounts are so small[7]. Secondly, it is hoped that the technique will eventually replace the need for animals to assess the PK/BA profile of chemicals at all[7,8]. Thirdly, the technique may lead to fewer drugs proceeding to safety tests in animals that (actually) have poor PK profiles in humans[2,7]. Currently this information is not known until after these trials and many animal lives are wasted on drugs that are never used in humans for this reason. However, it is important to note that microdosing is not currently anticipated to provide information on the safety or efficacy of chemicals[2].

How established is the technique?

The technique has been developed commercially in the UK by a company called Xceleron created by the University of York in 1997[10]. The effectiveness of microdosing using AMS was recently shown in an independent trial of five drugs selected for their particularly difficult ADME properties. The trial demonstrated a very promising 70% correspondence between microdose predictions and the outcome of pharmacological doses[5]. The EU is now backing this technology in a 2.1 million Euro research project called the EU Microdose AMS Partnership Programme (EUMAPP). The project involves 10 laboratories from 5 countries, and aims to boost expertise in microdosing and the application of AMS to developing new candidate drugs[11]. Microdosing has been endorsed by the European Medicines Agency[1], the US Food and Drug Administration[12] and there are increasing reports of its use within the pharmaceutical industry[13]. However, the assumption that the PK profile of a compound at microdose levels is the same as that at therapeutic levels still needs to be tested[7]. For example, compounds may be less soluble at higher concentrations which will affect their absorption in the body. Formal replacement of animals with human microdosing for this aspect of drug development has yet to occur but the future looks bright.

[8] Rowland, R. (2006) Microdosing and the 3Rs. Article for the National Centre for the Replacement, Refinement and Reduction of Animals in Research. See http://www.nc3rs.org.uk

[9] Combes, R.D. et al. (2003) Early microdose studies in human volunteers can minimize animal testing: Proceedings of a workshop organized by Volunteers in Research and Testing. European Journal of Pharmaceutical Sciences. 19; 1-11.

[10] See http://www.xceleron.com/

[11] See http://europa.eu.int/comm/research/headlines/news/article_06_01_20_en.html

[12] Food and Drug Administration 2006. Press release 12th Jan 2006: FDA Issues Advice to Make Earliest Stages Of Clinical Drug Development More Efficient See http://www.fda.gov/bbs/topics/news/2006/NEW01296.html

[13] Sandhu P, Vogel JS, Rose MJ, Ubick EA, Brunner JE, Wallace MA, Adelsberger JK, Baker MP, Henderson PT, Pearson PG & Baillie TA (2004) Evaluation of microdosing strategies for studies in preclinical drug development: demonstration of linear pharmacokinetics in dogs of a nucleoside analog over a 50-fold dose range. Drug Metabolism and Disposition 32 (11), 1254-1259