principally to German scientists, industries and government departments, and those provided by ECVAM, principally to European scientists and industries, and to other parts of the European Commission.

Professor Spielmann represents Germany in the ESAC, and, along with other members of the ZEBET staff, has been very active in ECVAM workshops and task forces.

There has also been funding by ECVAM of work at ZEBET, and support by ZEBET of work at ECVAM. The development of alternative databases is another area of co-operation.

However, the most significant result of the close co-operation between ECVAM and ZEBET has been the joint contributions made to the development of the concepts of prevalidation, validation and acceptance, and to the success of particular validation studies, notably, so far, those on phototoxic potential and skin corrosivity. Much more will be achieved in the future.

7 Concluding remarks

Somebody once said that the ECVAM workshops alone have provided several hundred recommendations about the development and application of scientifically advanced alternative methods – but who is going to see that they lead to action and to the gradual replacement of routine animal test procedures?

That is a good point, for talking is easy and inexpensive, whereas international co-operation is only of real value if it leads to definitive collaborative projects and to the accomplishment of genuine achievements.

The records of ZEBET and ECVAM, together and in association with many other partners, bear witness to this truth.

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The Funding of Research on the Three Rs in the EU

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Summary

In a number of European countries, notably Germany, The Netherlands, Sweden and the UK, there has been a significant commitment to research designed to achieve one or more of the Three Rs. This work has been funded by industry, by government, and by the animal welfare movement. The cosmetic industry, ZEBET in Germany and the Dutch Platform in The Netherlands, and FRAME in the UK, deserve particular mention. The European Commission also plays a major role, in two main ways. Firstly, research is supported via DGXII, particularly through programmes such as BRIDGE, BIOTECH and BIOMED in the Third and Fourth Framework Programmes (1991–1998). In the Fifth Framework Programme (1999–2002), major support for international collaborative studies on the development of replacement alternative test methods will be provided as parts of programmes concerned with the Cell Factory (novel in vitro testing as alternatives to animal testing) and Environment and Health (improvement of predictive toxicity testing, with emphasis on in vitro test systems and alternative screening and testing protocols). The second kind of funding is by competitive contracts for specific studies required by various Services of the Commission, including, for example, prevalidation and validation studies conducted for ECVAM.

Keywords: 3Rs, alternatives, animal procedures, funding, replacement, tests, validation

Zusammenfassung: Die Finanzierung der 3R-Forschung in der EU

Verschiedene europäische Staaten, vornehmlich Deutschland, Holland, Schweden und das Vereinigte Königreich haben für die Forschung, die eines oder mehrere Ziele der 3R anstrebt, grossen Einsatz geleistet. Finanziert wurden die Anstrengungen durch die Industrie, mit öffentlichen Geldern und durch Tierschutzorganisationen. Die Kosmetikindustrie und ZEBET in Deutschland, die Dutch Platform in Holland und FRAME im Vereinigten Königreich verdienen besondere Erwähnung. Eine Hauptrolle spielt die Europäische Kommission, und zwar in zweierlei Hinsicht: Einmal wurde die Forschung durch die DGXII, im besonderen durch die Programme BRIDGE, BIOTECH und BIOMED im dritten und vierten Rahmenprogramm (1991-1998) unterstützt. Im fünften Rahmenprogramm (1999-2002) wird die Hauptförderung für international koordinierte Studien zur Entwicklung von alternativen Testmethoden als Teil der The Cell Factory-Programme bereitgestellt, sowie bei Environment and Health, d.h. zu Verbesserungen in der Risikoabschätzung der Toxizität mit Schwerpunkten auf in vitro Testsystemen und für alternative Screeningverfahren und Testprotokolle. Die zweite Möglichkeit der Beschaffung von Fördermitteln ist die Ausschreibung von Forschungswettbewerben für spezielle Studien, die von verschiedenen Organen der Kommission angefordert werden, so z.B. auch Prävalidierungs- und Validierungsstudien für ECVAM.

1 Introduction

Not surprisingly, the reports of many ECVAM workshops, which are designed to review the status of Three Rs approaches in specific areas and to recommend ways forward, frequently refer to the need for further research and, either directly or by implication, to the need for the provision of adequate funding for this special purpose.

Since the active search for ways of implementing the Three Rs (reduction, refinement, replacement) concept of Russell & Burch (1959) gained momentum in the 1980s, partly because of new legislation, partly because of the increasing demands of the animal welfare movement, and partly because of increasing recognition by various industries of the benefits to be gained, various governments, industries and animal welfare organisations have specifically funded Three Rs-based research. Examples include the cosmetic industry, and the Dutch Platform in the Netherlands, FRAME in the UK, and ZEBET in Germany. In this brief note, attention will be focused on support given by the European Commission.

2 Funding of alternatives research by the European Commission

2.1 Funding via Directorate General (DG) XII

The main source of funding for alternatives research provided by the European Commission is via the international, shared-cost collaborative research programmes of DGXII, which is responsible for research, education and training in the European Union. Funding is allocated via a Framework Programme (FWP) system, which, throughout the 1990s, has recognised the significance of alternative methods. For example, the Third FWP (1991-1994) saw the BRIDGE programme, while the Fourth FWP (1995-1998) included BIOMED and BIOTECH. The BIOTECH projects which are nearing completion include studies on skin sensitisation, the blood-brain barrier, hepatotoxicity, nephrotoxicity, and teratogenesis, and on cell immortalisation. The BIOMED projects include studies on drug metabolism, neurotoxicity, phototoxicity, ocular toxicity, and pharmacokinetics.

The Fifth FWP (1999-2002) is now under way, and the programme on Quality of Life and Management of Living Resources involves two key actions of particular relevance to alternative methods.

Key Action 3: The Cell Factory includes action 3.13 *Novel In Vitro Testing as Alternatives to Animal Testing*, which lists the following as aspects for consideration: reinforcement of prenormative research by making cell cultures available as a substitute for animal testing; development of high throughput screening for detecting toxicity; an *in vitro* toxicity test, e.g. for local toxicity, immunotoxicity, neurotoxicity.

Key Action 4: Environment and Health includes part 4.2.2 *Improvement of predictive toxicity testing and mechanism–based risk assessment consistent with the aim of reduction and eventual replacement of animal testing*, in which the following areas for consideration are listed: to improve toxicological methods, with an emphasis on *in vitro* systems; alternative screening and testing protocols to arrive at better diagnosis of health effects and risk assessment of environmental substances or agents harmful to human health; investigations on intraspecies and interspecies variability, in order to limit uncertainties and to establish more-reliable data sets and to improve the scientific basis for extrapolation from animal and cell culture data to humans; and development of new screening and testing protocols with emphasis on the need to integrate endpoints.

In addition, the Quality of Life and Management of Living Resources programme refers to Research and Technological Development Activities of a Generic Nature which include the following: chronic and degenerative diseases; genomes and diseases of genetic origin; neurosciences; public health and health services research; persons with disabilities; and biomedical ethics – including an ethical framework for the life sciences: the involvement of human beings in research; the use of human tissues (including stem cells); the use of animals in research, especially non-human primates; and the ethical conduct of research.

2.2 The sigificance of DGXII support

The funding of shared cost research by DGXII is very significant, not only because of the opportunities it provides for collaborative research, especially on replacement alternative methods, but because of the language in which the policies of the Commission are expressed. For example, the eventual replacement of animal testing is recognised, as is the need for improvement of predictive toxicity and mechanism–based risk assessment This improvement will be based on an emphasis on *in vitro* systems, and alternative screening and testing protocols are needed to arrive at better diagnosis of health effects and risk assessment. The need to improve the scientific basis for extrapolation from animal cell culture data to humans is recognised, as is a need for the development of new screening and testing protocols, with emphasis on the need to integrate endpoints. These various points of emphasis should be seen as good news by replacement alternatives researchers (and by the animal welfare movement).

2.3 Funding by competitive contracts

DGXII also has other funding shared-cost action programmes, which may provide opportunities for research on alternatives, as well as other relevant programmes, e.g. for so-called demonstration projects to support new technology transfer. In addition, other Commission services, including ECVAM, conduct work via external agencies by competitive contract, according to specific requirements in the form of technical annexes produced by the Commission. Calls for tender are invited, usually as a result of published announcements in the Official Journal of the European Communities.

For alternatives researchers, the main DGs concerned are DGXI, which is responsible for Directive 86/609/EEC, for legislation concerned with the classification and labelling of potentially dangerous chemicals, and for the protection of the environment; DGIII, which is responsible for legislation concerned with

* Since these talks were given, the European Commission services have been recognised and renamed. DGIII is now known as Enterprise DG, DGXI as Environment DG, DGXII as Research DG, and DGXXIV as Health and Consumer Protection DG.

the manufacture and marketing of cosmetics, medicines and biological products (including hormones and vaccines), and DGXXIV, which is responsible for the protection of consumers.

2.4 Funding via ECVAM

ECVAM has a limited amount of funding for the support of external studies by contract, sometimes as a result of direct assignment, but usually following the publication of calls for tender in the Official Journal. These studies can involve reports (e.g. reviews on particular problems or tests), the preparation of methods for prevalidation, or prevalidation and/or formal validation studies. ECVAM publishes calls for expression of interest from time to time, in which institutions are invited to register their interest in working with ECVAM on particular topics. Contracts awarded by direct assignment can sometimes be based on the selection of institutions listed in this register.

ECVAM is able to support its own workshops and task forces, and can sometimes make contributions in support of scientific conferences.

Significant contributions were made by ECVAM in support of the successful validation studies on *in vitro* tests for phototoxic potential and for skin corrosivity, and ECVAM's current support of prevalidation/validation studies includes studies on the following topics:

- *in vitro* embryotoxicity tests;
- the GM–CFU test for a cuteneutropenia;
- *in vitro* models of the blood-brain barrier;
- *in vitro* tests for skin irritation;
- a reference standards approach to eye irritation;
- the quality control of batches of recombinant FSH; and
- the quality control and safety testing of various biologicals.

2.5 Significance of the role of ECVAM

Formal validation is a vital and inescapable step in the process whereby tests which are properly developed for particular purposes are shown to be reliable and relevant, before being accepted into regulatory practice.

The role of ECVAM, as a Commission service working in close collaboration with other Commission services, is of pivotal and crucial significance in the European Union, as has recently been emphasised by DGXII in describing the Quality of Life and Management of Living Resources part of the Fifth FWP (Figure1)

3 The importance of international collaboration

One of the great advantages of research funding via the European Commission is that, as in many other EU activities, international collaboration is not unusual, but is an everyday expectation. It brings added value to every research programme through the sharing of ideas and the contribution of complementary experience and expertise. This is proving to be particularly important in the development, validation and acceptance of replacement alternative test methods, where some formality and much independence of management are essential, because of the nature and importance of the decisions to be taken on the basis of the test results (Balls and Fentem, 1999). Replacement alternative methods are now beginning to successfully complete the scientific validation assault course, and this owes much to the contributions being made by ZEBET and ECVAM with their many partners in academia, government, industry and the animal welfare movement, not only in Europe, but also in the USA and in other parts of the world.

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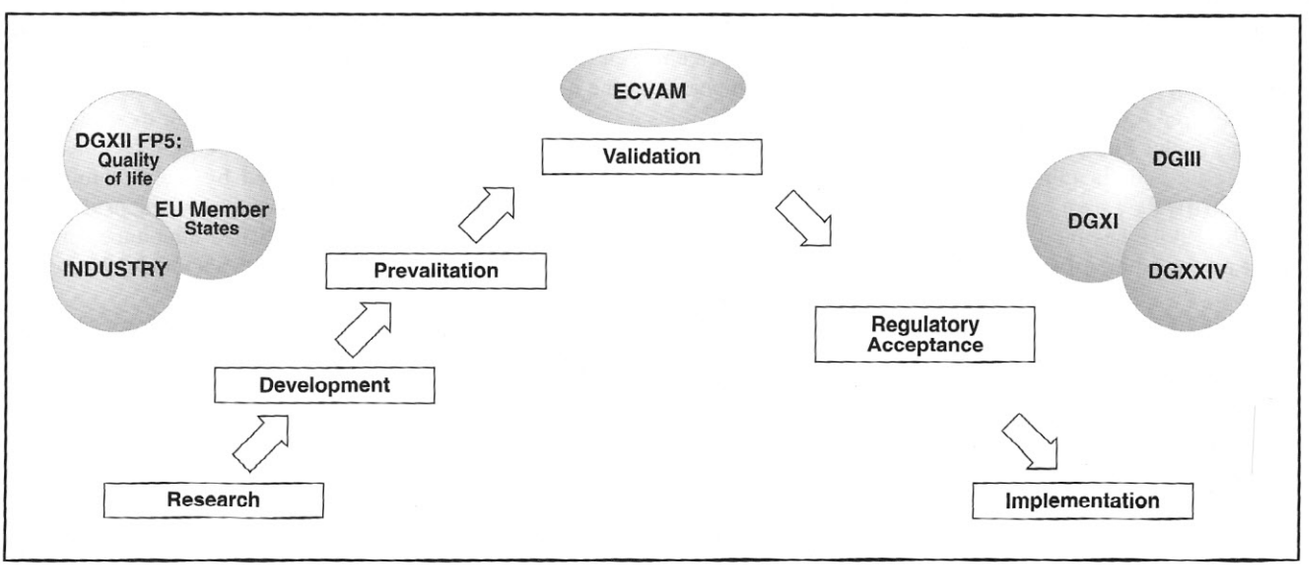

Figure 1: Key Steps and EU Players