



INSTITUTE FOR
HEALTH AND
CONSUMER PROTECTION



ACTIVITY REPORT
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EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

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The IHCP is located in northern Italy, on the lakeshore of Lago Maggiore (Varese province). The nearest city is Milan (approximately 60 km south-east), and the region is served by Malpensa International Airport, located at about 30 km from the JRC.

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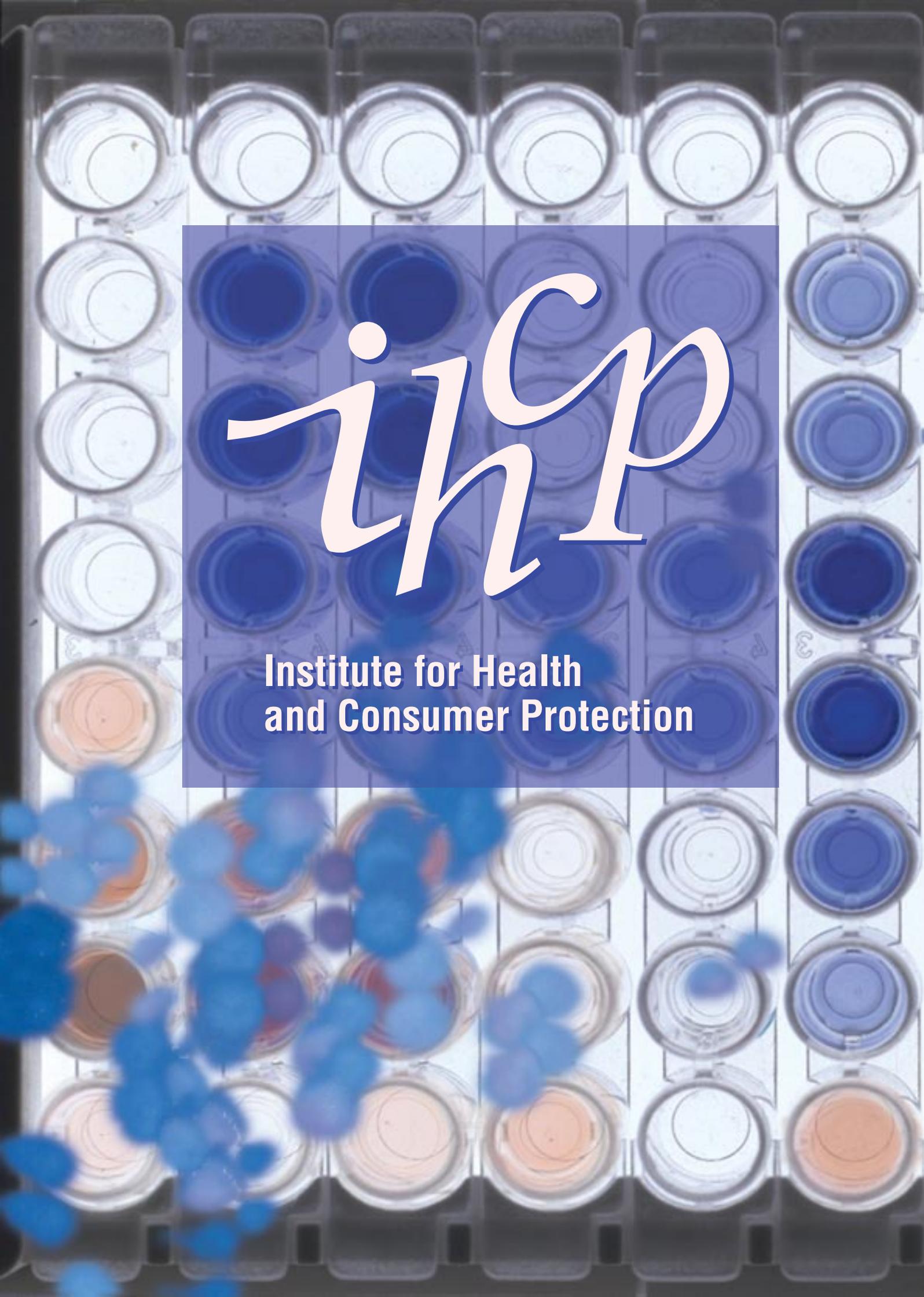
A large, stylized, light-colored graphic of a person in motion, possibly a runner or a person in a dynamic pose, is centered on a yellow background. The figure is composed of thick, rounded lines and is positioned behind the main text.

ihcp

Institute for Health and Consumer Protection
Activity Report 2001



EUROPEAN COMMISSION
JOINT RESEARCH CENTRE



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**Institute for Health
and Consumer Protection**

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Foreword

It is my pleasure and honour to take up my duties as the Director of the Institute for Health and Consumer Protection (IHCP) on January 15, 2002.

The year 2001 witnessed many scientific achievements and activities at IHCP, as can be seen in this report. The IHCP consolidated its position as a scientific reference and validation centre for food safety, genetically modified organisms (GMOs), and chemical substances. More specifically, the IHCP (along with the European Network of GMO Laboratories) has been recognised as the Community Reference Laboratory (CRL) on GMO detection and identification. The expanded European Chemicals Bureau will play a central role in the future EU chemical policy, with the strong co-operation of the European Centre for the Validation of Alternative Methods (ECVAM). Competencies in material and nuclear sciences are being explored further by the Biomedical Materials and Systems Unit in order to develop new applications in the medical and health sectors. The IHCP staff members take special pride in the remarkable record of accomplishment in 2001, and they intend to continue.

The IHCP has also contributed to the implementation of the European Research Area (ERA) through its extensive scientific networking, promotion of training and mobility of young and senior scientists, and enlargement activities. The aforementioned activities allow for the co-ordination of research and exchange of scientific and technical information among EU Member States and others. A number of training activities took place in 2001 at IHCP with the goal of transmitting specialised know-how to the Accession Countries and to assist in their implementation of EU legislation.

My arrival here also coincides with the challenging period of defining the JRC Multi-annual Work Programme (2003-2006) within the context of the 6th Framework Programme (FP6). This is an exciting opportunity to shape the future of the institute activities. IHCP activities clearly remain anchored in the core area of food, chemical products and health. An integrated scientific area approach is the key to success—our institute has already developed interdisciplinary approaches to a number of scientific areas.

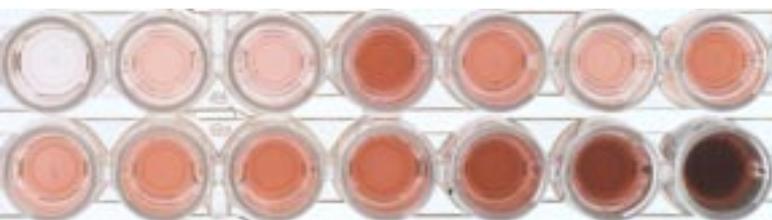
This report lays down the challenge for IHCP to generate scientific knowledge and to translate it into supporting policy-makers and citizens. The IHCP will continue to rely on science to solve health and consumer protection problems as they arise. I genuinely look forward to working closely with all of you in the months ahead.



*Kees Van Leeuwen
IHCP Director
March 2002*

IHCP Mission Statement

The mission of the IHCP is to provide scientific support to the development and implementation of EU policies related to health and consumer protection. The IHCP carries out research to improve the understanding of the hazards and health risks posed by food contaminants, chemicals, biocides, and biochemical systems.



Scientific Objectives

IHCP activities focus on the following scientific objectives:

- Assessment of the safety and quality of food, animal feed, and other consumer products (including genetically modified organisms)
- Development and validation of alternative testing methods to replace, reduce or refine use of laboratory animals in biomedical sciences
- Assessment of risks to health and environment from chemical substances, and management of related information service
- IT support to pharmaceutical regulatory activities
- Development, validation and use of advanced processing techniques and test methods for the qualification of biocompatible materials, medical devices, and health diagnostics.

End-users/Collaborations

IHCP's direct end-users are services within the European Commission. Moreover, IHCP collaborates with a large number of universities, industrial partners, Euro-

pean and national authorities, international organizations, and consumer associations (the following is a non-exhaustive list):

| | |
|------------------------|---|
| Customers (within EC) | <ul style="list-style-type: none"> • DG Agriculture, DG Environment, DG Enterprise, DG Consumer Protection (SANCO), DG Research, DG Trade, DG Taxation and Customs Union (TAXUD), DG Enlargement, European Anti-Fraud Office (OLAF) • DG JRC: EI (Ispra), IRMM (Geel), IAM (Petten), ITU (Karlsruhe), IPTS (Seville) • European Medicine Evaluation Agency (EMA) |
| Customers (outside EC) | <ul style="list-style-type: none"> • European Parliament • International organisations (i.e., OECD, WHO, FAO, Council of Europe) • European agencies (i.e., European Directorate for the Quality of Medicines (EDQM)) • Government (i.e., Competent authorities responsible for the implementation of biotechnology and novel food Directives; chemical authorities, pharmaceutical regulatory agencies in the European Economic Area (EEA), regulatory and health care authorities) • Non-governmental organisations (NGOs) • Industry (i.e., biotechnology, food and feeding stuff, chemicals, biomedical) • Consumer associations |
| Partners | <ul style="list-style-type: none"> • Universities • European Committee for Standardisation (CEN) • Government research centres • National laboratories (GMOs and Food, laboratories active in the field of <i>in vitro</i> techniques of the main European chemical, pharmaceuticals and cosmetics industries, biomedical laboratories) • Industry (GMO, food and feed, chemicals industry, biomedical) • Associations (such as COLIPA, ECETOC, EFPIA, EUCOMED, AOAC, IUPAC) |

Executive Summary



The IHCP was established in October 1998 through the re-organisation of existing expertise and structures within the JRC Institutes in order to provide a common framework for the more effective use of scientific competencies in the area of health and consumer protection. The IHCP carries out research to improve the understanding of the health hazards, exposure and risks posed by food contaminants, biocides, chemicals, and genetically modified organisms (GMOs), through the development, validation and application of advanced testing methods. The IHCP multidisciplinary environment makes it a unique place to promote the aims of the European Research Area (ERA).

Given the continuous policy concern regarding the safety and quality of food and consumer products, the IHCP has extended its activities in this area. In support of the Commission's White Paper on Food Safety and related EU legislation, the IHCP has *validated six analytical methods* in 2001 (i.e., the detection of central nervous tissue in meat products, the migration assessment of phthalates from toys). It has also *developed eight analytical methods* (i.e., the quantification of cocoa butter equivalents and polyphenols in chocolate, the determination of mycotoxins) that support the enforcement of certain EU Directives (i.e., the new European Chocolate Directive 2000/36/EEC). In the future, the IHCP intends to strengthen its involvement in the traceability of food and feed products, as well as the compilation of appropriate analytical methods for organic food.

Many consumers are concerned about the widespread use of GMOs as food and in food products. The EU has already adopted legislation for the approval to grow, import, and use GMOs as food or food ingredients. The IHCP has directly supported this legislation through the validation of sampling and detection methods of GMOs. In 2001, the European Commission has also recommended the JRC-IHCP, together with the European Network of GMO laboratories (ENGL), as the Community Reference Laboratory (CRL) on GMO detection and identification. The IHCP will continue to support EU policies in biotechnology related areas with an emphasis on the development, validation, and harmonization of analytical methods.

The new Chemicals policy aims to establish a single coherent regulatory framework for all chemical substances, and to reverse the responsibility for testing and risk assessment to industry. The European Chemicals Bureau (ECB) already provides technical and scientific support to a number of Directives such as 67/548/EC on Classification and Labelling, 93/67/EC on risk assessment of

new substances, 98/8/EC on Biocides. In 2001, the ECB introduced seven new testing methods, and fully risk assessed 15 existing substances (human health and environmental parts). The IHCP intends to play an important role in the chemical policy area through an expanded ECB, and ECVAM.

The European Centre for the Validation of Alternative Methods (ECVAM) was established by a Communication of the European Commission to the Council and Parliament (SEC/91/1794) to support the implementation of the Directive on animal protection (86/609/EEC). In 2001, ECVAM continued to play an important role at the international level in the development and formal validation of advanced alternative (non-animal) test methods for the toxicological assessment of various types of chemicals, and for the quality control and safety assessment of immunobiologicals. In fact, the ECVAM Scientific Advisory Committee (ESAC) endorsed three *in vitro* tests for embryotoxicity as scientifically valid and ready for consideration for regulatory acceptance by the European Competent Authorities and at the level of the Organisation of Economic Cooperation and Development (OECD). Moreover, ECVAM strengthened its role in the dissemination of knowledge information through the online availability of its databases on advanced methodologies as required by the Commission.

The IHCP continued to provide informatic support to the European Medicine Evaluation Agency (EMA) through EudraNet (EU Drug Regulatory Authorities' Network) – a service that supports the mutual recognition procedure for the authorisation of medicinal products. IHCP already began the transfer of EudraNet services to EMA, and foresees the outsourcing of the EudraTrack activity (a system for the support of mutual recognition) activity to a new operator at the end of 2002. In 2001, there was a further development of the Medicine Information Network for Europe (MINE1) as an interface application providing information that is tailored-based on specialized groups.

The Biomedical Materials and Systems Unit continued to develop, validate and use advanced processing techniques and test methodologies for the qualification of biocompatible materials, medical devices and health diagnostics (including medical applications of nuclear technology). In 2001, IHCP did extensive work on the development of plasma technologies for surface treatment, and testing methods of material release in order to improve the biocompatibility and reliability of medical devices. Such work supports the implementation of the Medical Device Directive (93/42/EEC) and the developing EU action programme on public health. Moreo-



Scientific Highlights in 2001

ver, the IHCP Cyclotron was designated as an official Marie Curie Training Site for biomedical testing using radiotracers, which will enhance training and technology transfer within the European Research Area (ERA).

Finally, the IHCP has contributed to the European Research Area through the establishment of European scientific networks in 2001. The institute has also extended its various European networks to include members from accession countries in light of the forthcoming enlargement. Moreover, the extensive European legislation directly related to the work of the IHCP (i.e., food safety, alternative methods, and chemicals) makes it highly relevant to the training of scientists from enlargement countries.



Food Safety and Quality

The Food Products Unit (FPU) has co-ordinated and finalised six international validation studies for the analysis of animal meat and bone meal and polychlorinated biphenyls in feeding stuff, brain in meat products, aflatoxins in food, and phthalates in toys.

The FPU has also improved eight methods of analysis for polychlorinated biphenyls (screening), wine authenticity, antioxidants in chocolate and mycotoxins and GMOs (extraction).

The FPU has carried out European monitoring studies for the determination of epoxidised soybean oil (ESBO) in baby food and mycotoxins in beer and has performed important work on sampling, as a new type of sampling lance has been constructed and patented. The lance will be tested for use as an alternative to classical and time/material consuming methods for mycotoxin analysis. The project was recognised with the JRC Innovation Project 2001 Award.

The FPU has prepared the grounds for laboratory accreditation according to international standards (ISO 17025) by establishing the appropriate in-house procedures and quality manual.

Genetically Modified Organisms (GMOs)

The GMO activity has gained high recognition through the work carried out in conjunction with the European Network of GMO laboratories (ENGL). This network was consolidated and formalised in 2001. Together with the network, the JRC will become the European Community Reference Laboratory (CRL) for the GMO food and feed regulation, when fully adopted.

A molecular register on GMOs has been set up to provide an on-line tool for analysis and interrogation of data. In addition, statistical strategies and considerations regarding sampling for GMO analysis have been developed that will help the understanding of sampling problems to GMO detection and quantification in food and raw materials.

Validation of Alternative Test Methods

ECVAM made significant achievements and strengthened its position as a well recognised international reference centre in the area of alternative methods. The ECVAM Scientific Advisory Committee (ESAC) endorsed three (alternative) methods for embryotoxicity testing (embryonic stem cell test, whole-embryo culture and

micromass assay) as scientifically valid and ready for consideration for regulatory acceptance.

A working group on chemicals was set up with the aim of producing a report to show how alternative tests and testing strategies could be developed and used in support of the future EU Chemicals Policy.

In line with its institutional commitments, ECVAM allowed first online access to its Scientific Information Service (SIS) via Internet at <http://ecvam-sis.jrc.it>. SIS is designed as a factual and evaluated (ready-to-use) information tool on various issues of advanced methodologies for toxicology assessments, including validation studies. As a test version, the first Internet version of SIS includes selected databases out of total data content of SIS.

ECVAM also established new cell culture laboratories, including facilities for ultratrace analysis for metals. A reporter gene assay has been established to detect cardiac toxicity due to chemical exposure in developing embryos during organogenesis, and a test system of genetically engineered cell lines has been finalised that considers inter-individual differences in human beings (polymorphism) for the study of metabolism-mediated toxicity. Significant progress was further made by characterising various cell lines of the haematopoietic system for protein expression and by establishing new endpoints to investigate nephrotoxicity *in vitro*.

European Chemicals Bureau

Numerous existing substances have been evaluated, bringing the number to a total of 67 priority substances since the beginning of the existing substances risk assessment programme.

In 2001, the ECB supported the implementation of the current legislation on dangerous substances through the finalisation of 15 comprehensive risk assessments (for both human health and environmental parts) of existing substances. The ECB also finished the human health (HH) part of five other risk assessments, but still needs to complete the environmental part.

In the same year, the ECB introduced seven new testing methods (TM) into Annex V of Directive 67/548/EEC. Two existing testing methods have been updated in order to keep up with the latest scientific developments. Moreover, the classical Lethal Dose (LD50) testing method was deleted from Annex V in order to reduce animal testing.

Five additional comprehensive EU Risk Assessment Reports were posted on the Internet, and were released for publication in 2001 as hard copy books.

Support to Pharmaceuticals

The SPR continued to provide support to EMEA (London). The outsourcing of the EudraTrack activity (a tracking system that permits the registration of procedures for marketing authorization through the mutual recognition process) to a new operator has been launched under the JRC Innovation and Technology Transfer programme, and is expected to be completed by the end of 2002.

The Medicine Information Network for Europe (MINE1) has been further developed into a centralized database service with all scientific, efficacy and safety information on medicine authorized within the EU.

Biomedical Materials and Systems

The plasma reactor for treatment of catheters based on a patented Transverse Flux plasma source was installed at the Ispra site.

A European thematic network (PLASMATECH) was set-up in 2001. The network will coordinate European activities in the field of plasma technologies in the areas of Health, Food and Environment.

A project "Immunoprobes for Food Contamination Analysis (IFCA)", in collaboration with the Food Product Unit, is due to start during spring 2002. The project will study and develop immunoprobes for analysis of patulin and mycotoxin.

There has been a transfer of the Photonics Sector to the BMS unit in order to consolidate activities related to optical diagnostics and medical imaging.

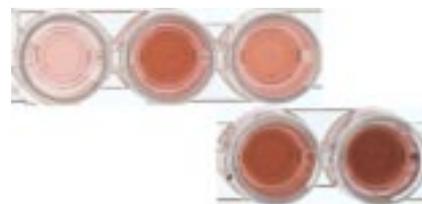
The IHCP purchased the surface characterization equipment (XPS/ToF-SIMS), which is a top-level system devoted to the chemical analysis of solid surfaces and thin films (elementary composition, quantitative analysis, imaging, chemical binding of single elements, chemical groups and molecules), as well as measurement of organic contaminants of surfaces. It is expected to be operative by the end of 2002.

A new radiopharmaceutical laboratory for the production of Flurodeoxyglycose (FDG) is being established at JRC Ispra.

The cyclotron was designated as an official Marie Curie Training Site for joint BMS/ECVAM activities on biomaterials testing using radiotracers.



The IHCP in Figures – 2001



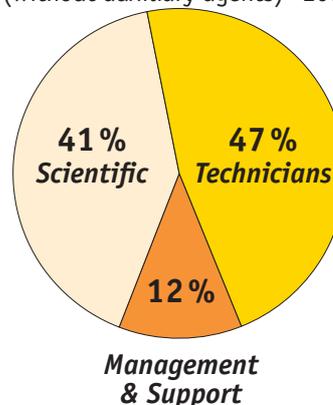
HUMAN RESOURCES

This section distinguishes the IHCP staff into statutory and collaborative staff (trainees, PhD and Post Doc grant holders, visiting scientists, national experts):

Statutory staff distribution – 2001

The DG JRC employs a total of **1,869** statutory staff (including officials, temporary agents, and auxiliary agents), and without auxiliary agents a total of **1,658**. Out of the total JRC staff, IHCP employs **171** statutory staff (including officials, temporary agents, and auxiliary agents), and without auxiliary agents a total of **141** staff members:

IHCP statutory staff
(without auxiliary agents) – 2001



| IHCP Statutory Staff (December 2001) | M | F | Total |
|--|-----------|-----------|------------|
| Officials | 37 | 19 | 56 |
| Temporary Agents on 5-year renewable contracts | 48 | 33 | 81 |
| Temporary Agents on 3-year non-renewable contracts | 2 | 2 | 4 |
| Total IHCP (without auxiliary agents) | 87 | 54 | 141 |
| Auxiliary Agents on 1-year non-renewable contracts | 8 | 22 | 30 |
| Total IHCP (with 30 auxiliary agents) | 95 | 76 | 171 |

Out of the total IHCP statutory staff (without auxiliary agents) 41% is scientific staff, 47% is technical staff, and 12% provides management and support. The IHCP scientific staff has significant expertise in a wide range of disciplines, such as Analytical Chemistry, Biology, Biometrics, Biophysics, Engineering, Food chemistry, Information technology, Science, Medicine, Pharmacology, Physics, Radiochemistry and Toxicology.

Collaborative Staff with Member States and Third Countries

The IHCP hosts a large number of collaborative staff (trainees, grant-holders, visiting scientists, seconded national experts) in order to adjust to its research activities. More specifically, the IHCP hosted **55** collaborative staff in 2001:

| IHCP Collaborative Staff (Dec. 2001) | M | F | Total |
|--------------------------------------|-----------|-----------|-----------|
| Trainees | 8 | 6 | 14 |
| Post-Graduate grant-holders | 3 | 15 | 18 |
| Post-Doc grant-holders | 4 | 7 | 11 |
| Visiting scientists | 2 | 5 | 7 |
| Seconded National experts | 4 | 1 | 5 |
| Total | 21 | 34 | 55 |

BUDGET

The EU Framework Programmes (FP) for Research and Development set out the general research priorities of the European Union in accordance with Article 169 of the EU Treaty. A total budget of €14,940 million was allocated to the Fifth Framework Programme–FP5 (1998-2002). The JRC (seven Institutes) received an amount of €1,020 million (7%) out of the total FP5 budget. The IHCP has been attributed an amount of

around €135 million for the period of 1999-2002 (around €33 million annually).

In general, IHCP credits come from the institutional budget (made available directly from the aforementioned European budget to the JRC); competitive activities; and associated states.

Institutional activities

The JRC defines its broad research areas into its multi-annual JRC Work Programme (1999-2002). The JRC Work Programme is updated annually (annual Work Programmes), and where appropriate, adaptations are made following exchanges with “customer” Directorate Generals to review progress and consider new needs. The 2001 JRC Work Programme is arranged according to the following programme lines: a) safety of food and chemicals, b) environment, c) dependability of Information Systems and Services, and d) nuclear safety and safeguards.

The majority of the IHCP projects contribute to the ‘Safety of food and chemicals’ programme line. The available credits to IHCP are divided into staff expenses, means of execution (maintenance of buildings and equipment, electricity, insurance, consumables, etc.) and operational credits (scientific acquisitions). The following table presents the IHCP institutional budget based on its projects in 2001:

| IHCP Institutional Budget 2001–Institutional Projects (K€) | | | | | |
|--|--|----------------|--------------------|----------------------------|---------------|
| | INSTITUTIONAL PROJECT | Staff expenses | Means of execution | Operational Appropriations | Total |
| | <i>Safety of food and Chemicals, and health related issues</i> | | | | |
| FPU | Control of Quality & Safety of Food & Related Items | 5,128 | 360 | 1,030 | 6,518 |
| FPU/GMO | Support to the Implementation of Community Policy on biotechnology (GMO) | 2,754 | 350 | 1,565 | 4,669 |
| ECVAM | Validation of alternative methods (ECVAM) | 5,319 | 100 | 1,975 | 7,394 |
| ECB | Chemical products, risk assessment (ECB) | 5,788 | 60 | 600 | 6,448 |
| BMS | Reliability of Biomedical Devices (REMEDI) | 5,575 | 40 | 400 | 5,705 |
| BMS | Minimally Invasive Medical Systems (MIMES) | 2,014 | 40 | 340 | 2,394 |
| | <i>Dependability of Information Systems and services</i> | | | | |
| SPR | Telematic system for the EU pharmaceutical regulatory activity (ETOMEPE) | 2,411 | 20 | 110 | 2,851 |
| Total | | 28,989 | 970 | 6,020 | 35,978 |

Competitive activities

The advantages of participating in competitive activities are that IHCP gains access to new expertise, and shares its own competencies and facilities. Competitive activities also provide another source of income besides the institutional budget. In accordance with JRC’s own regulations, competitive projects must complement the JRC’s mission and must respect the subsidiarity principle (*whereby the Union does not take action (except in the areas which fall within its exclusive competence) unless it is more effective than action taken at national, regional or local level*).

There are three types of competitive activities:

- Participation in shared-cost activities (SCA) with other successful consortia
- Activities financed in the context of other EU policies (non-research) upon request of other Commission services (OCA)
- Work undertaken for third parties on a contractual basis (TPW).

| Income from Competitive Activities (K€) | | |
|---|--------------|------------|
| Type | K€ | % |
| Shared Cost Actions (SCA) | 1,314 | 57 |
| Other Competitive Activities (OCA) | 922 | 39 |
| Third Party Work (TPW) | 100 | 4 |
| Total | 2,336 | 100 |

In 2001, the IHCP had 19 ongoing Shared Cost Actions out of which 13 started the same year. Most of the projects fall under the “Competitive and Sustainable Growth” programme while the remainder fall under the “Quality of Life” Programme. Moreover, the IHCP had one ‘other

competitive activity’ (OCA) on network services for the pharmaceutical regulatory sector, and one Third Party Work (TPW) agreement on the production of radioisotopes (¹²³I).

IHCP Organisational Chart



* Former IHCP Director F. Mc Sweeney became the JRC Director General in April 2001. Since then Mr. Mc Sweeney also served as acting Director of IHCP until December 2001. K. Van Leeuwen was appointed in December 2001, and commenced his duties in January 2002.

** G. Tartaglia served as head of the Management Support Unit during 2001. B. De Bernardi was appointed in December 2001, and commenced his duties in January 2002. MSU plays an overall ‘horizontal’ managerial, organisational, and coordinating role for the scientific activities of the institute.

f
pou

Food Products Unit





Web Information resources

At IHCP site:

<http://ihcp.jrc.cec.eu.int/Activities/ACTSafe/ACTSafe.html>

<http://ihcp.jrc.cec.eu.int/Activities/ACTGMOs/ACTGMOs.html>

At the FPU site:

<http://food.jrc.it/>

At the GMOs and Food Environment site:

<http://biotech.jrc.it/>

Food Products Unit (FPU)

The FPU activities focus on the development, harmonisation and validation of analytical methods for safety and quality assessment and compliance with labelling (including detection of fraud) of food, feed and other consumer goods. A section of FPU concentrates on genetically modified organisms in food and the environment. FPU's work is carried out to support the implementation of EC legislation.

Validation of analytical methods has remained a major issue for FPU, as well as training laboratory personnel from EU Member States and Accession Countries on various specific topics. The GMO activity has gained high recognition through the work carried out in conjunction with the European network of GMO laboratories (ENGL). The IHCP, assisted by ENGL, will become the *European Community Reference Laboratory (CRL)* for the GMO food and feed regulation, when it is fully adopted.

Closer collaboration with the Reference Materials Unit (RMU) of the JRC Institute for Reference Materials and Measurement (IRMM) has contributed to the corporate results of the JRC within the food sector.

The FPU is in the process of Accreditation according to ISO 17025 in order to comply with requirements for official food laboratories (accreditation expected to be received in 2002). The necessary laboratory quality manuals have been prepared. Laboratory procedures have been improved and a pre-accreditation audit of the laboratory has been carried out.

This chapter is divided into three sections related to specific activities of FPU: a) food and feed safety, b) food quality, and c) genetically modified organisms (GMOs).



FOOD AND FEED SAFETY

Animal meat and bone meal and specified risk materials

Meat and bone meal (MBM) in animal feed

The FPU took the initiative to develop and validate analytical methods in order to address requirements of European legislation against the spread of TSE. Activities in 2001 were as follows:

- Participation in the European shared cost action (SCA) project *Stratfeed*: The aim is to develop and validate methods in order to identify MBM in feed. In addition the FPU is investigating the suitability of other analytical approaches, such as pyrolysis GC/MS, for the detection of animal tissue in feed.
- Refinement and validation of a method for the determination of appropriate heat treatment of animal meal. This test requires the presence of bovine proteins in MBM and is considered complementary to another test validated by the FPU in 1999 that requires the presence of pork.
- The FPU has finalised a validation study for a method based on an immuno assay developed in the UK for the detection of heat stable proteins from ruminants and porcine in compound animal feed. In this evaluation, special emphasis was placed on the rendering conditions determining the applicability of the test and the sensitivity of the method.

Tissue of the central nervous system (CNS) in meat products

The FPU continued its recently started activity on the detection of tissues of the central nervous system (CNS) banned when specified as risk material (Commission Decision 2000/418/EC and its amendment Commission Decision 2001/2/EC) or labelled when used as an ingredient in meat products (Commission Decision 2001/101/EC amending Commission Decision 2000/13/EC). Several markers can be used to detect the presence of CNS tissues, among them some proteins such as Neuron Specific Enolase (NSE), Glial Fibrillary Acidic Protein (GFAP), and fatty acids such as nervonic acid. The main activities were:

- Validation of two immunochemical methods commercially available as test kits. The methods differ in their methodology and in the protein used as marker. The outcome of the international collaborative study shows that both methods can detect CNS in processed food.

- Development of a method based on LC-GC to determine nervonic acid. Parameters concerning HPLC pre-separation, interface and GC analysis were studied to obtain high sensitivity and resolution of the fraction of interest.



Animal fat from fallen stock in food and feed

Safe removal from the food chain of animal fat that is not fit for human consumption requires the use of appropriate marker substances. The need for such markers derives from the risk of mixing this type of animal fat with other animal fat originating from healthy animals. The latter type of fat is allowed to be used as an ingredient in the food and feed industry. Upon request of DG Health and Consumer Protection (SANCO), the FPU started to look for an appropriate marker, selecting and evaluating a triglyceride (trienantine) as candidate substance.

Residues and Contaminants

Polychlorinated biphenyls (PCBs) and dioxins

In 1999 the FPU had already started to develop analytical methods that meet the criteria of simplicity and robustness as a follow up to the Belgian dioxin crisis. In 2001 the focus was on the following two aspects:

- The optimisation of the extraction step, which is considered to be the bottleneck of rapid analysis. FPU showed that modern extraction techniques, such as pressurized liquid extraction, could circumvent the limitation of conventional extraction methods.
- The coordination of a European ring trial for the determination of PCBs in feeding stuffs.
- The FPU initiated a validation study of a screening method based on cell lines (CALUX), which is already in use in some laboratories for routine analyses.

Mycotoxins in food and animal feed

A project with a novel approach for the sampling of dry and unpacked food products (e.g. corn, coffee and cocoa) was initiated. The method is based on the fact that mycotoxins (and the responsible mould) can be found on the surface of contaminated food items. The approach is based on sampling the surface rather than the whole item. A new type of sampling lance has been constructed and patented. Due to the prospective importance of this challenging approach, the project was recognised with the 'JRC-Innovation Project 2001 Award'. The lance will be tested for use as an alternative to classical and time/material consuming methods within this project.

New derivatisation strategies were developed for an existing method for the determination of fumonisins in corn resulting in better analytical results. A European survey on the contamination of beer with various mycotoxins has started and includes the application of new multi-method approaches. A validation study of an analytical method suitable for developing countries to determine aflatoxins in food by thin-layer chromatography (TLC) has started. This includes the production of homogenised material (corn and peanuts), a pre-collaborative trial and the statistical evaluation of the method.

As thin layer chromatography (TLC) is a very simple, robust and easily applicable approach, its suitability for the analysis of various mycotoxins is under investigation (e.g. fumonisins, sterigmatocystin). In addition, alternative extraction methods are used for mycotoxin analysis (e.g. for zearalenone).

A multimedia CD has been produced for analysts who are engaged in mycotoxin analysis. The CD contains descriptions of methods that were the subject of validation studies, as well as training videos and a multimedia slide show. In addition, the whole CD contents (including the videos) were published on the FPU webpage (<http://food.jrc.it/>).

Several laboratory technicians from EU accession countries have been trained in the FPU laboratory on various state-of-the-art techniques for mycotoxin analysis.

Statistical concepts

Since 1996 all EU Member States have participated in a co-ordinated mandatory monitoring programme for the determination of pesticides in food. Specific pesticides and food items have been selected for this exercise. The FPU is contributing to this study by performing the statistical evaluation of the sampling programme.

The FPU also develops modified concepts such as factor statistics and examines whether the proper use of recovery data could improve method performance characteristics and the selection of laboratories that perform well.

Allergens

Reports on the prevalence of food allergies are sometimes controversial, but a significant number of people do suffer from allergies. There is a strong need for more precise methods of diagnosis and more efficient therapeutic methods. Better understanding of the allergens is needed for both purposes, especially on their formation and degradation during food processing and digestion. New legislation can be expected in the future regarding labelling of allergens.

The FPU organised an international workshop on food allergy in 2001 to discuss these issues and to prepare scientists to work jointly on these problems (EUR 20241 EN, 2002). The FPU has also initiated the assessment of test kits for the detection and determination of allergens and will expand this work in the future.

The FPU's GMO group organised an international workshop to discuss the development of a genetic database of known protein allergen sequences. The GMO group will establish the database in collaboration with Member State laboratories.

Contact materials

Migration of substances

Epoxidised soybean oil (ESBO) is used as a plasticiser in PVC-lined closure gaskets for e.g. baby food glass jars. Two EU Member States have recently reported on the high level of ESBO. The FPU completed a European Survey on more than 250 jars to evaluate the levels of contamination of ESBO in baby food. Research has also been initiated on the potential degradation of ESBO into chlorohydrins derivatives and to devise analytical strategies for their analysis.

The FPU continues to monitor and validate methods regarding the migration of substances used in organic coatings and lacquers for food cans such as bisphenol A diglycidyl ether (BADGE). Furthermore, the FPU chairs a CEN group (European Committee for Standardisation) dedicated to the development and validation of a multi-analyte method. Preliminary studies on matrix stability and homogeneity have been conducted in 2001 prior to a EU-wide validation.

Some volatile and semi-volatile components can migrate from packaging materials into dry foodstuffs as they do in liquid foodstuffs, albeit by different mechanisms. Thus specific migration testing methods should be de-

veloped for dry foodstuffs. The FPU undertook a compilation of pertaining data and initiated a systematic study in collaboration with industries that will target both polymeric materials and paper and board materials. The FPU has also initiated a compilation of state-of-the-art analytical approaches and the formation of an emergency expert network to draft method requirements for migration of compounds from isocyanates-based laminating adhesives used in food packaging.



A rapid screening method was developed, which confirmed to screen for contaminants from polyethylene terephthalate (PET), within the frame of a European shared cost action project. The mechanism of migration behaviour from paper and board contaminants to dry food (either through the vapour phase or by direct contact) was also studied.

On-line dissemination of information

In order to provide a public service source of relevant information, an on-line Internet site dedicated to food contact materials was created (<http://cpf.jrc.it/webpack/>) in 1998 in collaboration with DG SANCO and underwent a major expansion in 2001. Substances are held in a centralised databank at the JRC and are available to the public.

Release from consumer goods: toys

Phthalates are typically used as softeners in soft PVC toys and childcare articles and have been the subject of recent renewed health concerns. The FPU has optimised and harmonised two dynamic migration methodologies. The validation study was completed in 2001. Further research on the effect of the nature and concentration of phthalates, as well as of the manufacturing processes on release, performed in tandem with a Member State laboratory, was also completed.

FOOD QUALITY

Chocolate

The new European Chocolate Directive (Directive 2000/36/EC) allows the addition of up to 5% of vegetable fats other than cocoa butter in chocolate products.

As the indication on labels that vegetable fats other than cocoa butter have not been added to chocolate products is not precluded in the new Chocolate Directive, very sensitive methods are needed to assess compliance with labelling. The minimum detectable level of cocoa butter equivalents in mixtures with cocoa butter have been investigated by the FPU by using a simple, robust method developed in-house for triglyceride analysis.

Following the results of a competitive project for DG Enterprise (the final report was established in 1999) the work on preparation of a cocoa butter standard for analysis has been finalised. Specialised laboratories from various organisations (producers of chocolate and cocoa products, official control laboratories, universities) participated in a certification study carried out in 2001. The material was prepared in collaboration with the IRMM. Homogeneity studies of the samples have been finalised within the FPU and a final workshop to discuss the certification results was held in July 2001. The material will soon be made available to the public by IRMM and will serve to facilitate analysis.



Cocoa is rich in polyphenols that are thought to have beneficial physiological effects on the human organism (e.g. antioxidative, anti-inflammatory). Analytical methods have been developed in-house not only to identify and quantify such compounds in chocolate but also to analyse biomarkers in human fluids (especially urine).

Isotopic techniques for determination of authenticity

BEVABS-EU Wine Databank

In addition to the validation of the isotopic data vintage 1998, a number of important achievements have been reached, which improve the European measurement system in the field of isotopic measurements in wine, spirits and other food products. One major achievement in 2001 was the official adoption of the method proposed by BEVABS for the measurement of the carbon 13-isotope ratio in wines by the General Assembly of the International Wine and Vine Office (OIV) in October 2001. The method is now applicable for the control of the international wine market commercial



products. This method will also be included in the official EU wine control methods and this isotopic parameter will also be included in the EU Wine databank.

Reference materials

Five new Certified Reference Materials (CRM) were established covering the main applications in the area of quality control of wine, spirits and fruit juices with use of isotopic techniques. These new CRM were sent to the IRMM where they are now available for laboratories carrying out isotopic determinations in food and beverages. The use of these CRM for calibration and quality control in Member States control laboratories will contribute to greatly improving the comparability of the measurements in this sector.

Vegetable fats and oil

Various isotopic methods have already been investigated in-house over the past years for their suitability for the quantification of foreign oils in olive oils. These methods

are under further evaluation in recently initiated shared cost action projects (e.g. on hazel nut oil in olive oil, spreadable fats).

Training and networking

In 2001, three state laboratories from EU accession candidate countries (ACC) joined the proficiency testing of food analysis with isotopic techniques (FIT-PTS), thus extending the network of control laboratories in this area to 26 (18 EU, 3 ACC, 5 non-EU). JRC scientific staff visited the labs in Portugal and Greece, which will take over the tasks of isotopic measurements for food control in these countries. Austrian authorities have also been contacted for establishing transfer of know-how in this area. As a follow up, training of scientific staff from Member States and from accession candidate countries will be organised in 2002.

Furthermore, a number of shared cost actions relevant to the wine sector or to the control of food products with isotopic techniques have been initiated in 2001.

Organic Food

The FPU has started a feasibility study on the work to be performed on organically produced food. The FPU will focus on the distinction between conventional and organic food. The compilation of appropriate analytical methods is underway. The FPU's expertise in analytical methodology may help to develop or improve and to validate suitable approaches, for example, the assessment of the type of fertilizer used for produce, or the absence of animal proteins in diets of grassland raised animals. Organic food will be an important subject for the JRC in the near future.

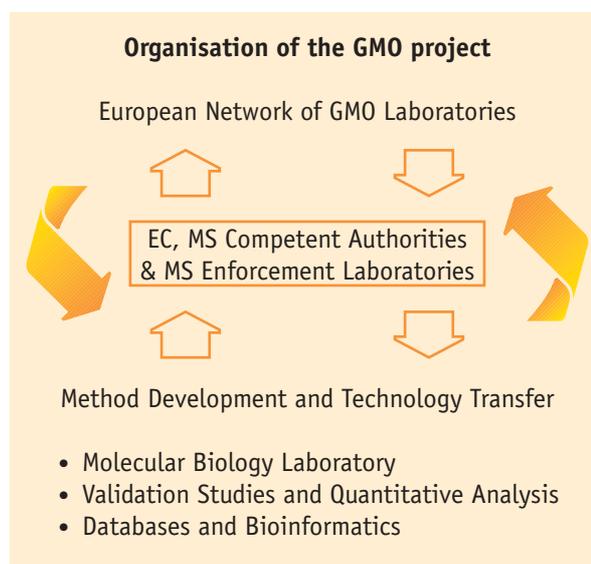
GENETICALLY MODIFIED ORGANISMS (GMOs)

From European Network of GMO Laboratories to European Community Reference Laboratory

The European Network of GMO Laboratories (ENGL) was set up in 2000 and is coordinated by the JRC, upon the request of EU Member States. The ENGL is a unique platform for 65 experts appointed by EU Member States and Accession Countries who have scientific and technical responsibilities related to GMO sampling, detection, identification and quantification, in the environment, food, feed and seeds. Moreover, efforts are being made to globalise the network: non-EU participants are also invited depending on the topics under discussion.

Two plenary ENGL meetings and a number of working group sessions were held in 2001. Major working areas include method development for qualitative and quantitative analysis, molecular biology technology transfer, validation and proficiency studies, reference mate-

rial, sampling strategies and procedures, and databases and bio-informatics.



Access to analytical methods and to appropriate test material is indispensable for enforcement laboratories. Therefore, IHCP is negotiating material transfer agreements with the major GMO producers to provide ENGL members access to appropriate control samples.

Both the Commission and Council have recognized the importance and value of ENGL, and proposed the IHCP, assisted by ENGL, to become the *European Community Reference Laboratory (CRL)* for the GMO food and feed regulation, when it is fully adopted.

Sampling and Validation Studies

Sampling research

Significant progress was made in 2001 concerning the understanding of the sampling problem related to GM detection and quantification in food and raw materials. In addition, support was provided both to DG-SANCO and to CEN TC275/WG11, where standards related to sampling for GM material are still under development. The work comprised of:

- Problems related to heterogeneity of GM material in large lots of raw (bulk) materials. Work is in progress that utilises statistical simulation, to better understand the importance of the various parameters involved: level of GM presence, clustering of material, size of the sample and the manner in which is made.
- Strategies for sampling final food units: a proposal has been made to consider the implementation of ISO approaches for sampling, that would permit a more powerful assessment of GM presence in large batches, using a standard quality assurance approach.

Both these subjects will be fully studied in practical test-case studies.



Validation Studies

As with the sampling work discussed above, results of the validation studies have been reported to the European Network of GMO Laboratories as well as to CEN (TC 275/WG11). Focus was placed on a method for quantifying GM-maize using real-time PCR and for quantifying GM-soybean in processed feed fractions using immunological techniques. In addition, a method for determination of T25 maize in pre-extracted DNA samples was validated during 2001.

Method development and proficiency tests

Detection methods

Efforts were made to develop GMO detection and identification methods that are at the same time event-specific, highly sensitive and straightforward in their application. For this reason a number of systems based on nested, semi-nested and multiplex PCR were studied and the possibility of their application investigated. As a result, detection and identification of all maize (Bt 176, Mon 810, Bt11, T25), and Roundup Ready soybean specific events currently approved for commercialisation in Europe is routinely performed. Application of a large variety of primers in direct and nested PCR allowed detection and identification at percentage GMO content limit of 0.05% 0.01% (LOD).

Quantitative methods

The introduction of the so-called "threshold regulation" (EC No 49/2000), stipulating the mandatory labelling of food products with a GMO adventitious content greater than 1%, made it necessary to have new, reliable, and powerful analytical methods. To address this need, particular attention was given to the development of quantification methods by means of Real-Time PCR. This technique allows the quantification of a spe-

cific sequence based on the measurement of the amount of fluorescence signals produced during amplification by GMO-specific fluorogenic probes during amplification of a PCR product as it accumulates.

Probes and primers suitable for the quantification of widespread events (CaMV 35S promoter and nos-terminator, sequences present in the vast majority of the GM products approved in Europe) and specific events (maize Bt176, maize T25 and soybean Roundup Ready) have been made available.

Studies have been undertaken with the aim to develop quantification systems that would be further tested for their performance in pre-ring trial schemes.

A database on methods for the detection, identification and quantification of GMOs has been established. This prototype database is designed to allow direct and user-friendly access to information. See <http://biotech.jrc.it/documents/documents.asp> and <http://biotech.jrc.it:591/GMOmethods.htm>.

GMO Proficiency Testing and participation in validation studies

The GMO laboratory was actively involved as a partner in a number of proficiency studies and collaborative studies for GMO detection and quantification. Qualitative and quantitative DNA (PCR, nested-PCR, Real-Time PCR) and protein-based (ELISA test) analyses were performed on several test materials to assess the presence, the combination and the specific GM event(s) and quantify the level of genetically modified ingredients present.

Make DNA extraction less hazardous with better performance

A non-commercial (CTAB) protocol currently in use in GMO laboratories was optimised in order to obtain an extraction method providing acceptable integrity, purity, quality, and quantity of a DNA template from variable sources for a subsequent GMO detection. The aim was also to develop a chloroform-free CTAB based extraction method.

In addition, potential inhibitors of PCR (e.g. chemical substances used during the extraction of DNA or compounds from the food matrices) were identified and determined.

GMO Reference Materials

The GMO group had a close collaboration with IRMM for the development and testing of new Certified Reference Materials (CRMs). In particular, a new series of Roundup Ready soya beans flour, denominated IRMM 410S (GM

percentage: 0%-0.1%-0.5%-1%-2%-5%) was tested by quantification based on Real Time PCR and data on GM percentage, homogeneity of the samples, possible contaminations were provided to IRMM.

Informatics support as an underpinning tool for ENGL

Database on field release studies

The GMO sector has a history of informatics support to Commission policies. An example is the ongoing activity on the management of the application summaries of small-scale field trials carried out in the Member States involving GMO's. Since the implementation of the GMO Directive 90/220/EEC, IHCP has received and circulated over 1.700 dossiers. In the near future, the IHCP will collaborate with the Institute for Prospective Technological Studies (IPTS) on a review of the data contained within the database. Moreover, a comprehensive review paper will be produced, describing the content of the database.

Biosafety Clearing House

The IHCP has been invited to participate as an expert in meetings of the Biosafety Clearing House, operating under the Biosafety Protocol. This worldwide regulatory framework (the "Cartagena Protocol") foresees an exchange of information when so-called living modified organisms are transported across national borders. The system designed by IHCP and implemented in the EU Member States may serve as an example for such global information exchange mechanism.

GMO Bulletin board

In support to the ENGL, a bulletin board has been created that is accessible on the Web only by members of ENGL and by Commission representatives where they can download all meeting documents and where they can post questions, comments or answer enquiries of colleagues.

Molecular register

A molecular register is essential to store all the molecular data known about a GMO and to build an interface in order to analyse molecular sequences and to compare them with the massive amount of sequences that are stored in gigantic databases such as EMBL. In collaboration with two Member State laboratories, the IHCP has embarked on a two-year project, which foresees the establishment of such a molecular register that also links with other databases and provides the on-line tools to analyse and interrogate the data. This initiative matches Commission needs, as outlined in Directive 01/18/EEC, in which it is stated that a molecular register should be established.



SUPPORT TO CEN (European Committee of Standardization)

In 2001 the Food Products Units actively participated in the following Technical Committees (TC) and Working Groups (WG):

- CEN/TC 275 (Food analysis – horizontal methods)
- CEN/TC 275/WG 5 (Mycotoxins)
- CEN/TC 275/WG 11 (Genetically Modified Organisms)
- CEN/TC 194 (Materials and articles in contact with food) – four working groups.

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Wollgast J., Pallaroni L, Agazzi M-E. and Anklam E. (2001). "Analysis of procyanidins in chocolate by reversed phase high performance liquid chromatography with electrospray ionisation mass spectrometry and tandem mass spectrometric detection", J. Chromatogr. A 926, 211.

INSTITUTIONAL PROJECTS

- Control of Quality and Safety of Food & Related Items
- Support to the Implementation of Community Policy on biotechnology (GMO)

SOME SHARED COST ACTIONS

- Food safety: STRATFEED, SIMBAG-FEED
- Food Quality: MEDEO, GLYCEROL, COFAWS, WINEDB
- GMOs: QPCRGMOFODD, ENTRANSFOOD

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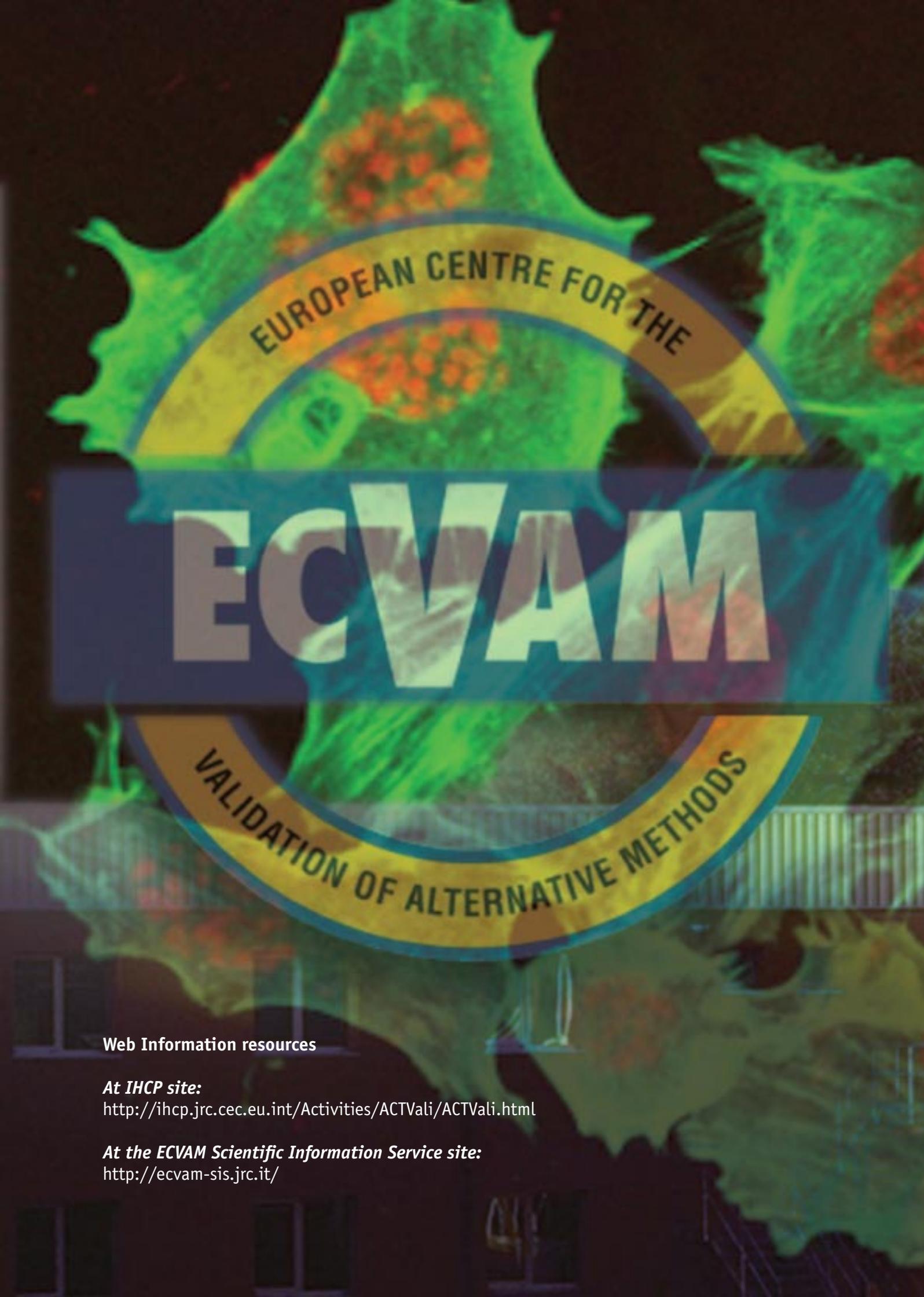
Food Quality

Chocolate & Organic food & Allergens
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Isotopic techniques and BEVABS
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Genetically modified organisms

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EUROPEAN CENTRE FOR THE

ECVAM

VALIDATION OF ALTERNATIVE METHODS

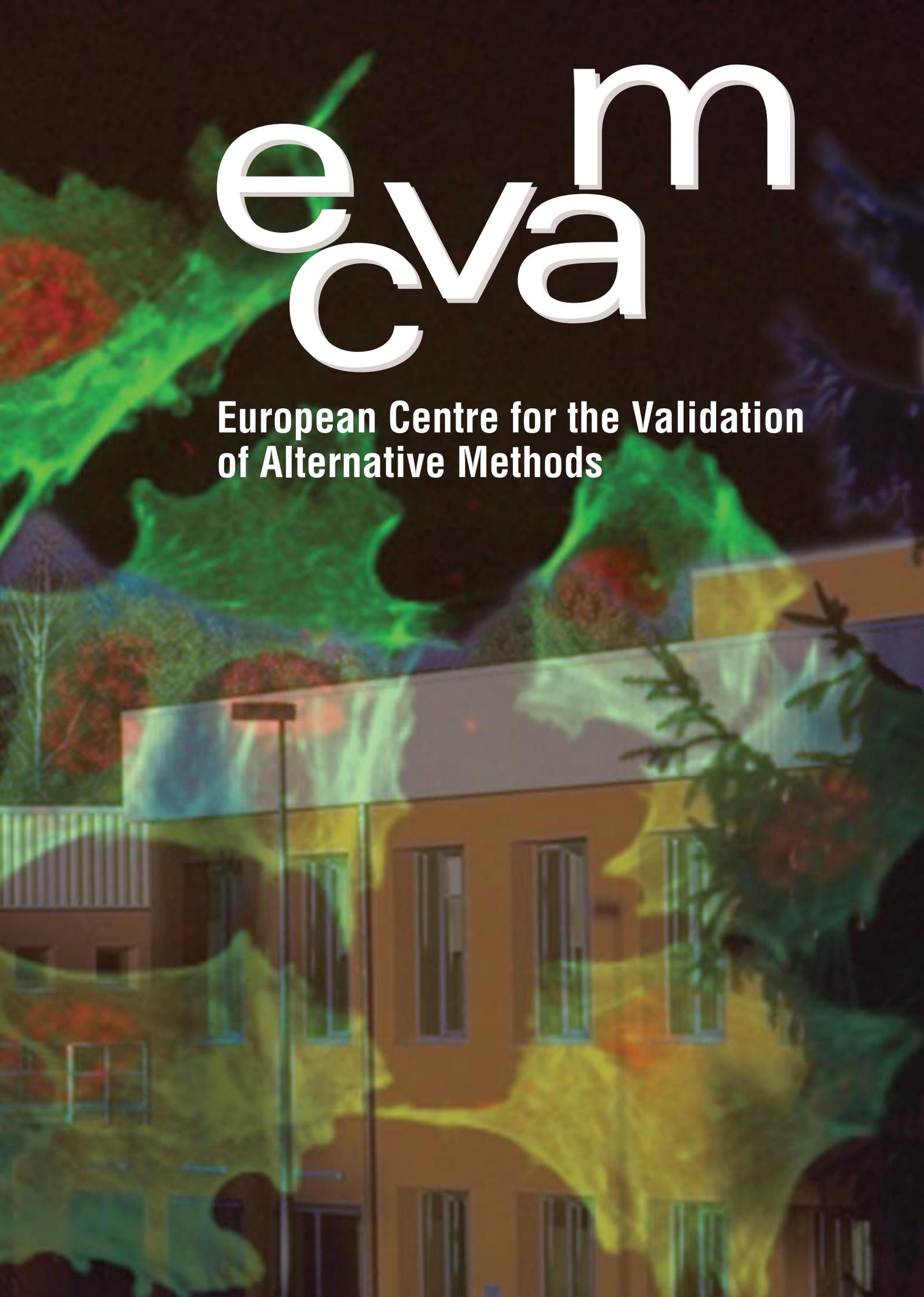
Web Information resources

At IHCP site:

<http://ihcp.jrc.cec.eu.int/Activities/ACTVali/ACTVali.html>

At the ECVAM Scientific Information Service site:

<http://ecvam-sis.jrc.it/>



ecvam

**European Centre for the Validation
of Alternative Methods**

European Centre for the Validation of Alternative Methods (ECVAM)

The Validation of Alternative Biomedical Test Methods

The European Centre for the Validation of Alternative Testing Methods (ECVAM) is an international reference centre for the development and acceptance of alternative testing methods to replace, reduce or refine use of laboratory animals in the biomedical sciences with an emphasis on toxicological assessments. ECVAM was established by a communication of the European Commission (SEC 91/1794) referring to a requirement in the animal protection *Directive 86/809/EEC*.

ECVAM's work is focused on the development and evaluation of *in vitro* methods (e.g. cell and tissue cultures), the use of computer modelling based on structure-activity relationships, and on physiological and biokinetic modelling. ECVAM's role is to co-ordinate international validation studies, to act as a focal point for the exchange of information, to set up and maintain a database on alternative methods, and to promote dialogue among legislators. Moreover, ECVAM plays an active role in the pre-normative research activities of the JRC.

Due to the political sensitivity of its duties, ECVAM, uniquely at the JRC, has its own Scientific Advisory Committee (ESAC) with participation from all Member States, relevant industrial associations, academic toxicology, the animal welfare movement, as well as other Commission services with an interest in the alternatives topic area.

Consequently, ECVAM has established a wide international network of collaborators in the Member States, and all over the world. ECVAM also works in close collaboration with other Commission services, such as DG Environment, DG Enterprise, DG Research and DG Health and Consumer Protection.

The validation process

Serious decisions must be taken on the potential effects of various kinds of chemicals and products. Therefore, the validation of new methods requires a formal process, usually involving the blind testing of coded test items in a number of laboratories, with independent selection and coding of these items, and independent collection and analysis of the test results. This part of the process is preceded by a confirmation that a method has been satisfactorily developed to meet certain criteria, and a pre-validation stage to assure that an opti-

mised test protocol is available and can be transferred from one laboratory to another. It is followed by an independent evaluation of the outcome of the validation stage (e.g. by ESAC), then consideration by the appropriate regulatory bodies in the Commission and the Member States.

Two important reviews were published in order to explain ECVAM's principles and procedures of validation: one on the role of prediction models in validation (Worth & Balls, 2001a), and another one on ECVAM's role in promoting the regulatory acceptance of alternative test methods (Worth & Balls, 2001b).

Within this context, at its 17th Meeting in October 2001, ESAC endorsed three alternative methods (embryonic stem cell test, whole-embryo culture and microassay) for embryotoxicity testing.

Also in 2001, an ECVAM staff member, Andrew Worth, represented the Commission on the Steering Committee for the *OECD Conference on Validation and Regulatory Acceptance of New and Updated Methods in Hazard Assessment* to be held in 2002.

In this chapter ECVAM activities are separated into the following areas: a) laboratory-based tasks, b) non-laboratory tasks, c) the ECVAM scientific information service (SIS), and d) other activities.



LABORATORY-BASED TASKS

Carcinogenicity and Metal Toxicity

Trace metals and their compounds constitute a risk to public health. Their possible harmful effects due to environmental, occupational and biomedical exposure (induction of toxic, mutagenic and carcinogenic effects) are addressed in a series of Directives (80/778, 80/1107, 87/416, 89/458, 91/441, 2001/466), and in recent proposals for amendments of Directives (such as the Annex II of Directive 2000/53/EC).

In 2001, screening studies were completed on Balb 3T3 mouse fibroblasts for the determination of the carcinogenic potential of 58 inorganic compounds; basal cytotoxicity of at least 30 metal compounds via a *test battery* including dog epithelial renal cells (LLC-PK1 and MDCK); rat pheochromocytoma (PC12) and immortalised human keratinocytes (HaCaT) as a model for nephrotoxicity, neurotoxicity and dermal toxicity.

Furthermore, the set-up of a number of laboratories and facilities were completed: a cell culture laboratory for metabolic studies, radiochemical facilities, and a laboratory for ultratrace analysis by advanced spectrochemical techniques (GFAAS-FCP-MS) of metals in growth media and cell cultures.

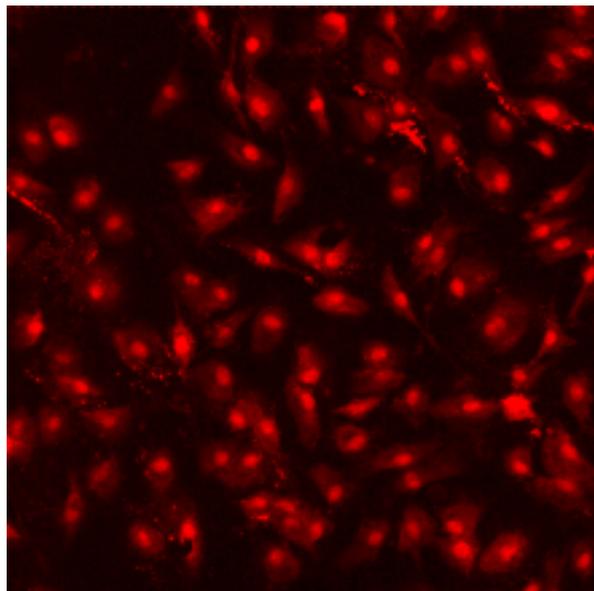
Haematotoxicity and Anti-Cancer Drugs

Damage to the blood-forming system is an important aspect of the toxicity of many types of chemicals and products, including industrial chemicals, medicines, and pesticides. The aim of developing alternative methods in this branch of toxicology is to predict the potential adverse effects of xenobiotics on human haemopoietic targets under controlled experimental conditions in the laboratory.

In 2001 the final report on the successful validation study of the CFU-GM clonogenic *in vitro* test to predict *in vivo* acute neutropenia has been submitted for publication. In the meantime, the optimisation of protocols of BFU-E/CFU-E clonogenic assays has been carried out.

New molecular endpoints have been used to evaluate modifications in primary human bone marrow cultures, spontaneously occurring or after treatment with agents with different mechanisms of action: telomerase activity, p53 status, the proneness to undergo apoptosis and changes in the karyotype have been investigated.

Characterization of cell lines for proteins expression was done, as well as the selection of key genes for the haemopoietic stem cell gene expression. There is an ongoing evaluation of p-53 mutations and cell cycle modulation after chemical exposure.



Human endothelial cells from smooth muscle of aorta.

Metabolism, Neurotoxicity and Immunotoxicity

Metabolism is the process by which an administered chemical is structurally changed in the body by either enzymatic or non-enzymatic reactions. Information on the metabolism of a substance is important in the evaluation of toxicological data. Test methods were established using genetically engineered mammalian cell lines harbouring mainly human drug metabolising enzymes for studies of metabolism-mediated toxicity, inhibition and the detection of inter-individual differences after chemical challenge (polymorphism).

In the absence of any validated *in vitro* method for evaluating the neurotoxic hazard of a chemical, increasing efforts were undertaken in this area to further develop and refine test systems by using the in-house patented genetically modified PC12 neuronal cell line.

Furthermore, at present, there is a lack of human cell-based assays that can predict the toxicity of chemicals towards the immune system in a simple, fast, economical, and reliable way. Whole blood cytokine release models have attracted increasing interest and are broadly used for pharmacological *in vitro* and *ex-vivo* studies, as well as for the pyrogenicity testing (used as one of the test systems in the FP5 Shared Cost Action (SCA) project "Comparison and Validation of Novel Pyrogen Tests Based on the Human Fever Reaction"). At ECVAM these methods were adapted for immunotoxicity testing, allowing potency testing of immunostimulating and immunosuppressive agents.

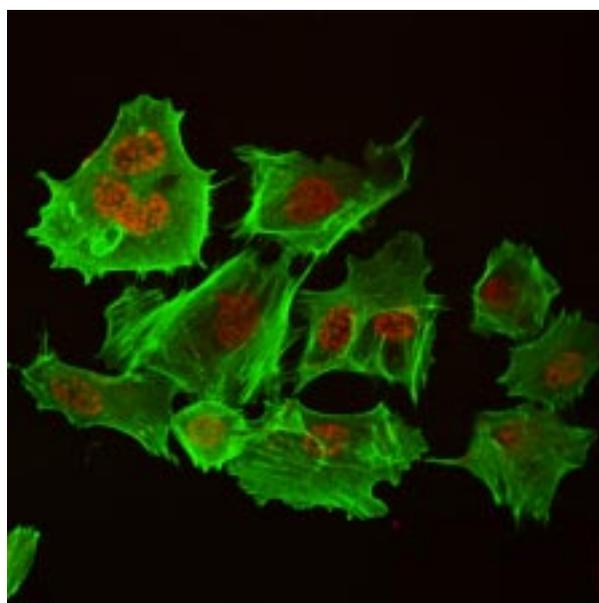
Nephrotoxicity, Barriers and Long-Term Toxicology

Cellular barriers play an important role in many organs of the human body by regulating the uptake, transport and secretion of endogenous and foreign chemical substances. *In vitro* tests are being developed at ECVAM and with collaborators, for detecting toxicity to various barriers, e.g. the renal epithelium, the intestinal epithelium, the blood-brain barrier and the skin after short and long-term exposure to potential toxicants.

A project on “Prevalidation of trans-epithelial resistance and inulin permeability as endpoints in *in vitro* nephrotoxicity testing” is in progress. In addition, ECVAM has been investigating the molecular and cellular mechanisms involved in damage caused by toxicants to renal tubular epithelial cell lines. Several flow cytometric and confocal microscopic endpoints have been established with collaborators for studying nephrotoxicity *in vitro* (Alvarez-Barrientos *et al.*, 2001).

Two long-term *in vitro* toxicity systems, a flow cell bioreactor and a static cell bioreactor, have been tested and compared with the use of conventional cell culture flasks. The results have been presented in the ETCS Congress in Granada, Spain.

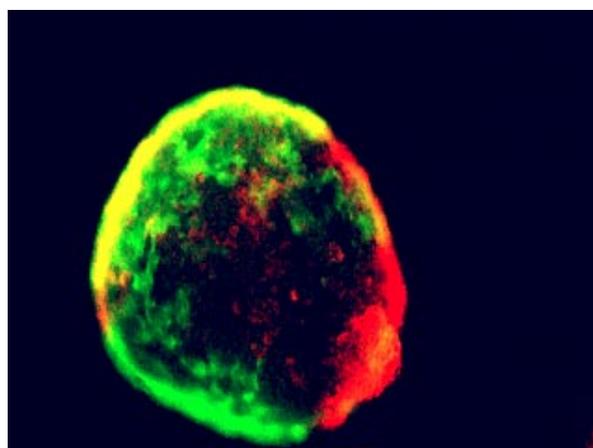
A study on *in vitro* models for the blood-brain barrier has been completed.



Immunofluorescent staining for acting microfilaments (green) and nuclei (red) of CdCl₂ treated LLC-PK1 cells.

Reproductive Toxicology and Cardiotoxicity

Embryotoxicity is an important part of reproductive toxicity testing since the thalidomide disaster has demonstrated the sensitivity of the developing embryo to chemicals. After a successful validation of the embryonic stem cell test ECVAM has focused on the further development of the reporter gene assay in order to get information about chemical effects on the different target tissues during organogenesis. This issue is especially interesting for pharmaceutical industry to test structure derivatives of drug candidates with a teratogenic potential. A preliminary prediction model has been developed in order to obtain information about developmental cardiotoxicity (Bremer *et al.*, 2001). Drug candidates have been tested by using the reporter gene assay, and a good correlation between *in vivo* and *in vitro* experiments could be demonstrated. In addition, genetically engineered embryonic stem cells have been established providing information on chemical effects on the endodermal differentiation. The data resulted in an award for the best poster presentation in the 2001 MEGAT Congress in Linz, Austria. Furthermore, a combination of a biotransformation system and the reporter gene assay has been established in order to detect pro-teratogenic compounds. The results have been presented in a thesis of an ECVAM trainee (Cristian Pellizzer) and received the maximum points possible by the University of Varese, Italy.



Cell aggregate consisting on genetically engineered embryonic stem cells.

NON-LABORATORY TASKS

Biologicals

Biologicals are products such as vaccines, immunosera, immunoglobulins, hormones, monoclonal and polyclonal antibodies, which play an important therapeutic and preventive role in human and animal health care. Due to their origin and the used production techniques, these biologicals undergo extensive quality control during their production. In particular, each batch of the finished product is tested for purity, safety and potency, which often involves the use of large numbers of animals. ECVAM participates and supports pre-validation and validation studies on Three Rs (Reduce, Refine, Replace) methods for the quality control of biologicals.

In 2001, two studies, namely the prevalidation of physicochemical methods for the potency testing of recombinant follicle stimulating hormone and the study on the relevance of the target animal safety test for the batch testing of veterinary vaccines have successfully been finalised. ECVAM currently supports the validation of a cell culture method for specific toxicity testing of diphtheria vaccines and it regularly comments on the European Pharmacopoeia monographs in order to reduce, refine or replace the use of animals in the quality control of biologicals.

In the field of biologicals, ECVAM mainly collaborates with the competent authorities of the EU Member States, the European Pharmacopoeia, industry, and the Advisory Group on Alternatives to Animal Testing in Immunobiologicals (AGAATI).

Computer modelling

Computer based systems for predicting toxic effects are likely to play an important role when the emerging EU Chemicals Policy is implemented by means of new legislation. Therefore, there will be a strong need for the development and validation of such computer-based systems. In 2001, ECVAM continued with research on the development of structure-activity relationships (SARs) for acute local toxicity, on the development of prediction models for embryotoxicity, and on the application of statistical methods in *in vitro* toxicology, such as bootstrap re-sampling.

Human Studies and Topical Toxicity

An extended ECVAM Skin Irritation Task Force meeting was held to follow-up the ECVAM pre-validation study, and to prioritise the activities required prior to setting up a validation study on alternative methods for acute skin irritation (Zuang *et al.*, 2002).

In the context of ECVAM's initiative on the EU chemicals policy, a report on the current status of alternative tests for eye irritation was prepared. Several recommendations were made, amongst which the acceptance of some well-established alternative methods for eye irritation on a weight-of-evidence approach and the harmonisation of the acceptability of these methods within the different Member States.

A survey was conducted within industry to establish the worldwide use of the neutral red release (NRR) assay. A review of the NRR assay, including the outcome of the survey was published (Zuang, 2001).

A report on the *Current Status of the Development and Validation of Alternative Methods of Interest to the Cosmetics Sector* was prepared for DG Enterprise/F/3. This report is a part of the annual report related to cosmetics testing, that DG Enterprise/F/3 has to prepare to comply with the requirements of the *Cosmetics Directive 76/768/EC*. Comments on proposals for a seventh Amendment to the Cosmetics Directive were provided to DG Enterprise/F/3 and to the JRC hierarchy.

An update on ECVAM's work was given at the Scientific Committee on Cosmetology and Non-Food Products (SCC-NFP; DG SANCO/C/2) subgroup on alternatives meeting.

THE ECVAM SCIENTIFIC INFORMATION SERVICE (SIS)

In line with its institutional duties, ECVAM established the scientific information service (SIS) to disseminate factual and evaluated (ready-to-use) information on advanced alternative methods for toxicology assessments. SIS mainly provides full method descriptions, including their development and validation status, test protocols for their performance, and information on test results.

This year has seen the completion of the first online Internet version of SIS that includes selected databases out of the total data content of SIS. The aim of this first release was to provoke constructive comments on the proposed structure, content, and planning of the database.

At the same time, the information content of SIS is continuously being updated in various fields of *in vitro* toxicity testing carried out in collaboration with various European Institutes.

With the aim to further improve the retrieval of information on alternatives in databases, the first phase of the *ECVAM Thesaurus on Advanced Alternative Methods (TAAM) project*, a systematically ordered collection of harmonised terms, has been concluded. This project was a result of a collaboration with the Head of the Thesaurus section of the US National Library of Medicine, the world leading authority in the area of thesauruses applied to biomedical sciences.

OTHER ACTIVITIES

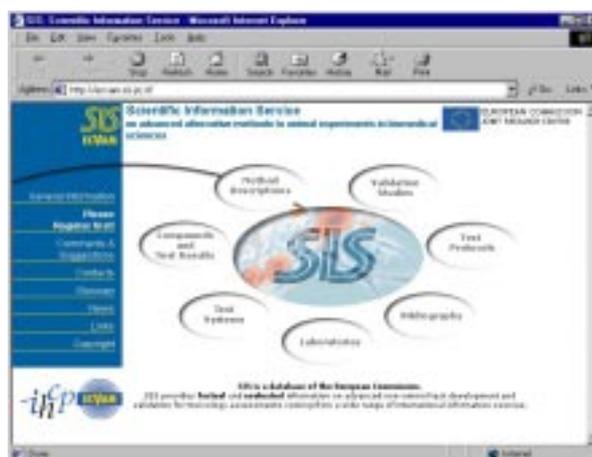
ECVAM Workshops & Task Forces

ECVAM workshops are held to review the current status of various types of alternative tests and their potential uses, and to identify the best way forward. Task Forces focus on more tightly defined targets. In 2001 the reports and recommendations of 4 Workshops have been published in the scientific journal *Alternatives to Laboratory Animals* (copies of reprints can be obtained from ECVAM) and another 6 ECVAM workshops and two task force meeting have been held.

Good Laboratory Practices and Good Cell Culture Practices

The maintenance of high standards is fundamental to all good scientific practice, and is essential to ensuring the reproducibility, reliability, credibility, acceptance and proper application of any results produced.

At ECVAM, further efforts have been undertaken to reduce uncertainty in the development and application of *in vitro* procedures by promoting international harmonisation and standardisation of various laboratory practices. This is done through the establishment of the, so called, *Good Cell Culture Practices (GCCP)* along the principles of the Good Laboratory Practice (GLP). These principles laid down in the ECVAM workshop nr. 37 are currently further discussed with the OECD GLP working group.



SIS Home page: <http://ecvam-sis.jrc.it>

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INSTITUTIONAL PROJECT

- Validation of alternative methods

SHARED COST ACTION

- Comparison and Validation of Novel Pyrogen Tests based on the Human Fever Reaction

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Web Information resources

At IHCP site:

<http://ihcp.jrc.cec.eu.int/Activities/ACTChem/ACTChem.html>

At the European Chemicals Bureau site:

<http://ecb.jrc.it/>





ecb

European Chemicals Bureau

European Chemicals Bureau (ECB)

The ECB provides scientific and technical support to the conception, development, implementation and monitoring of EU policies on dangerous chemicals. The ECB supports the development and harmonisation of testing methods; the legal classification and labelling (C&L) of substances; the management of risk assessment of substances; the notification of new substances; the authorization of dangerous biocides; and the information exchange on import and export of dangerous substances. Directives supported are 67/548/EEC, 93/67/EEC, 96/56/EC, 97/56/EC, 98/8/EC and the regulations are 2455/92, 793/93, and 484/94.

Main partners of the ECB are the authorities of the EU Member States and Norway, Commission services (such as DG Environment and DG Enterprise), the chemical industry, and NGOs. The ECB manages and chairs around 40 meetings per year with the aforementioned stakeholders.

The New EU Chemicals Policy

The recent White Paper on the Strategy for a future Chemicals Policy (COM (2001) 88 final) presents the Commission proposals for a new EU chemicals policy. The IHCP (the ECB and ECVAM) will play a central role in the establishment of this policy through the:

- Further expansion of activities in this field including the responsibility for approximately 100,000 registrations on 30,000 chemicals;
- Establishment of a central system of **Registration, Evaluation, and Authorisation of Chemicals**—the so-called REACH-IT system—to host all chemicals data and to support the authorities of the EU Member States;
- Restriction and authorisation procedure on chemicals of high concern; and
- New testing strategy using alternative tests.

Moreover, a large amount of information on the use and exposure of substances will be given to the enlarged ECB by the down-stream users.

The following sections will focus on a) the process of the evaluation of (existing and new) substances; b) the authorization of biocides; and c) the information exchange on import/export of dangerous substances.

THE PROCESS OF THE EVALUATION OF SUBSTANCES

There is an arbitrary distinction between ‘existing’ and ‘new’ substances in Europe, which affects the evaluation process. Existing substances are defined as those substances that were already on the EU-market, and listed in the European Inventory of Existing Commercial Substances (EINECs) by 18 September 1981—an inventory containing 100,106 substances. New substances are those placed on the EU market for the first time after 18 September 1981. These new substances must be notified before being placed on the market, after which they are registered in the European List of Notified Chemical Substances (ELINCs).

In contrast to the new substances, existing substances have never been subjected to a systematic testing regime. When the requirement for testing and notification of ‘new’ substances was introduced in 1981, substances already on the market were exempted. Only in 1993, the Council Regulation 793/93 introduced a framework for the evaluation and control of ‘existing’ chemical substances, thereby complementing the already existing rules for new substances governed by Council Directive 67/548/EEC. The newly proposed EU chemicals policy would like to eliminate the distinction between the two (existing and new) substances.

| Relevant EC legislation on Substances | |
|---------------------------------------|--|
| Directive 67/548/EEC | Classification & Labelling, Notifications, Testing Methods |
| Directive 93/67/EEC | Risk Assessment New Substances |
| Directive 98/8/EC | Biocides |
| Regulation (EEC) 793/93 | Existing Substances |
| Regulation (EC) 1488/94 | Risk Assessment Existing Substances |
| Regulation (EEC) 2455/92 | Export/Import |
| Directive 76/769/EEC | Restriction on Marketing and Use |
| Directive 91/414/EEC | Plant Protection Products |

The ECB supports the three first steps of Council Regulation EEC 793/93: data collection, priority setting, and risk assessment of substances. In consultation with EU Member States the Commission must regularly draw up lists of priority substances, on the basis of collected information, taking into account their potential effects to humans or the environment. The following subsections describe in more detail the stages of the evaluation process of substances.

The harmonization of Testing Methods

Harmonized testing methods must exist in order to evaluate the properties of various substances. The ECB is responsible for the technical and scientific work needed for the development, introduction, and adaptation to technical progress of testing methods of Annex V to Directive 67/548/EEC (and its adaptations). Annex V contains standardized testing methods for the determination of the intrinsic properties of chemical substances, which allow for the characterization of potential hazards for people and the environment. Data provided by testing methods constitute the basis for a proper classification and labelling of chemicals and for risk characterization. Moreover, the use of these standardized methods ensures the mutual acceptance of data, and the free circulation of goods between countries. The ECB activities in this area are coordinated with the OECD and other international organizations.

In 2001, the main achievements in introducing or updating testing methods were the:

- Deletion of Method B.1 (the classical LD₅₀ method) from Annex V during the 28th Adaptation to Technical Progress (ATP). This is a major achievement for animal welfare.

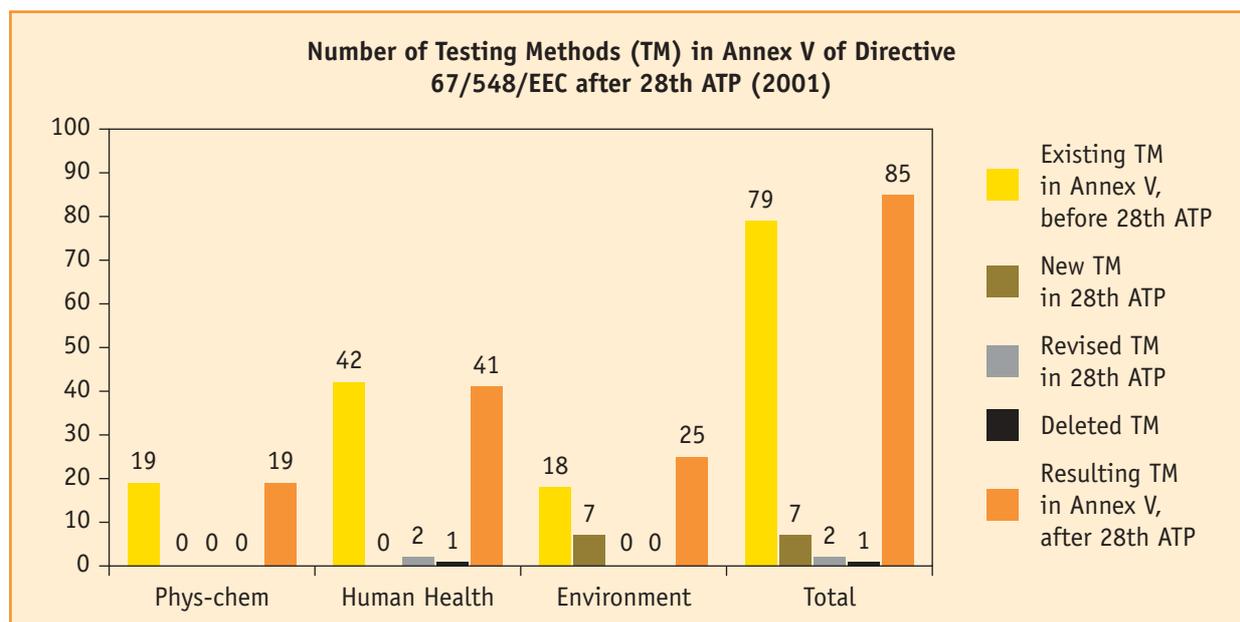
- 7 new testing methods were introduced into Annex V at the 28th ATP. Two other testing methods were revised.
- Further development of testing methods for Man Made Mineral Fibres (MMMF): Presentation of the first phase of the 90 days inhalation study to the National Co-ordinators and the CMR groups, 2 papers on MMMF published, method to determine the Length Weighted Geometric Mean Diameter of fibres (LWGM) in advanced stage.
- 7 new or updated testing methods ready for a forthcoming ATP.
- 5 additional new or updated testing methods (including some alternative) in advanced stage.

The figure below shows the total number of testing methods for physico-chemical properties, toxicological effects and eco-toxicological effects as in Annex V of the Directive 67/548/EEC.

Legal classification and labelling (existing and new substances)

The ECB is in charge of technical and scientific issues for the Adaptation to Technical Progress (ATP) of Annexes I, II, III, IV, VI, and IX to Council Directive 67/548/EEC on the classification, packaging and labelling of dangerous substances. The ECB's work entails the preparation, chairing and follow-up of meetings of the Commission Working Group on Classification and Labelling (composed of experts from EU Member States and observers from the EEA Member States, industry and NGOs); the co-ordination of meetings between EU Member States and industry; and the provision of information to other Commission services.

The 28th ATP was published in August 2001. The new ATP includes—besides testing methods—an updated



foreword to Annex I (the list of classified and labelled substances) together with 352 new and 139 revised Annex I entries. It also includes an updated and consolidated version of Annexes II, III, IV and VI of the Directive, i.e. the hazard symbols, risk and safety phrases and the complete classification and labelling criteria. The preparation of the 29th ATP started during 2001 as well as a new consolidated version of Annex I.

A technical working group, chaired by the ECB, was set up to prepare the implementation of the Globally Harmonised System (GHS) of classification and labelling within the Community in the context of the White Paper on a future chemical policy.

Risk assessment for existing chemicals and new chemicals

All substances (existing and new) on the priority list must undergo an in-depth risk assessment to examine the risks posed to humans and the environment (terrestrial, aquatic and atmospheric eco-systems). The risk assessment follows the framework set out in Regulation

1488/94, and implemented in the detailed Technical Guidance Documents on Risk Assessment for New and Existing Substances.

The first draft of the risk assessment reports are prepared by the Member State which acts as 'rapporteur', and is submitted to the Technical Meetings for discussion. The ECB mediates the technical meetings, which attempt to reach consensus on the conclusions of the risk assessment. After adoption of the risk assessment, three publications are produced:

- Comprehensive risk assessment report (3 formats): book, IUCLID, and ECB homepage
- Summary (2 formats): book and ECB homepage
- Conclusions in the Official Journal or the European Communities.

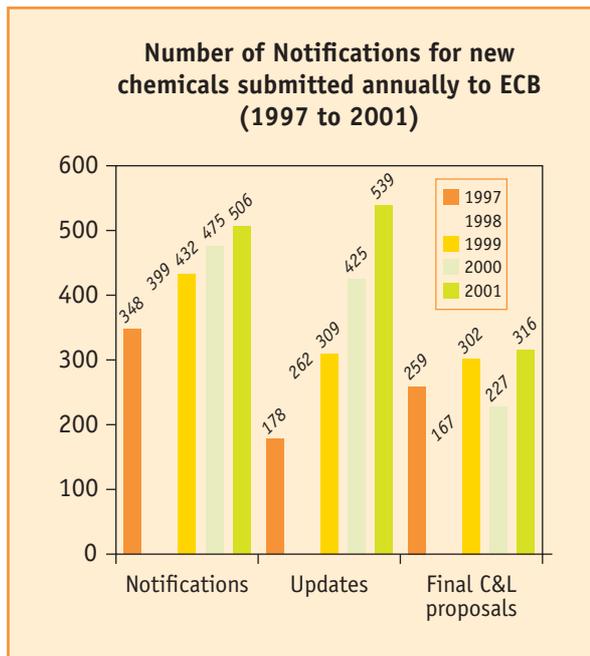
i) Existing chemicals

The following table shows the risk assessment reports of existing substances that were finalised in 2001, and the Member State that acted as 'rapporteur'.

| Risk assessment reports of existing chemicals finalised in 2001 | | |
|---|------------|--------------|
| SUBSTANCE | CAS N> | Member State |
| 1-vinyl-2-pyrrolidone | 88-12-0 | UK |
| 2-furaldehyde | 98-01-1 | NL |
| 4,4-isopropylidenediphenol | 80-05-7 | UK |
| Ammonium dichromate | 7789-09-5 | UK |
| Benzyl butyl phthalate | 85-68-7 | N |
| Buta-1,3-diene | 106-99-0 | UK |
| Cromium trioxide | 1333-82-0 | UK |
| Edetic acid | 60-00-4 | D |
| Methylenediphenyl diisocyanate | 26447-40-5 | B |
| Pentane | 109-66-0 | N |
| Potassium dichromate | 7778-50-9 | UK |
| Sodium dichromate | 10588-01-9 | UK |
| Tetrasodium ethylenediaminetetraacetate | 64-02-8 | D |
| Trichloroethylene | 79-01-6 | UK |
| Trizinc bis (orthophosphate) | 7779-90-0 | NL |
| Zinc | 7440-66-6 | NL |
| Zinc chloride | 7646-85-7 | NL |
| Zinc distearate | 557-05-1 | NL |
| Zinc oxide | 1314-13-2 | NL |
| Zinc sulphate | 7733-020 | NL |

Main achievements in 2001 were:

- Numerous existing substances have been risk assessed, bringing the number to a total of 67 priority substances since the beginning of the existing substances risk assessment programme.
- Five additional comprehensive EU Risk Assessment Reports were posted on the Internet, and were re-released for publication in 2001 as hard copy books.
- The Technical Guidance Documents revisions for the Risk Assessment of New Notified, Existing Substances and Biocides were finalised at technical level at the Joint TM in October 2001.
- Version 4.0 of the International Uniform Chemicals Information Database (IUCLID) was released in May 2001. IUCLID is a database that allows the collection and exchange of data required for risk assessment within the EU chemicals programme. The database was developed by ECB in close cooperation with industry and EU Member States.
- Three ECB training courses on IUCLID and EU risk assessment procedures were carried out in 2001.



ii) Risk Assessment on new chemicals

Since 1983, the authorities of the EU Member States carried out risk assessments for more than 1000 new substances (out of the total 5000 submitted notifications for over 3300 substances), mainly above 1 ton per year.

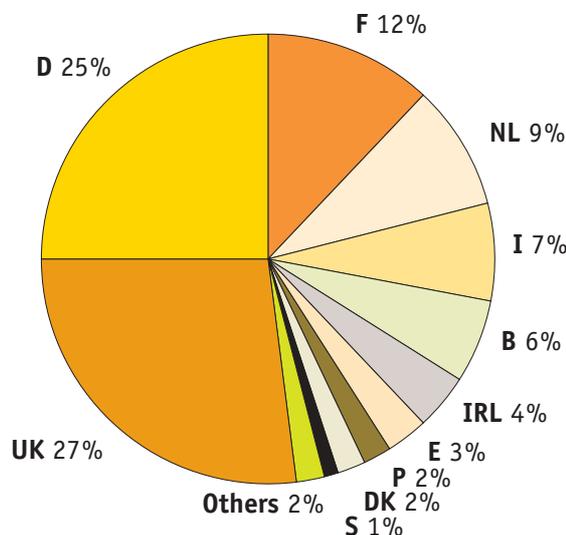
The notification of new chemicals

All new chemicals have to go through the notification (and risk assessment) process, as laid down in the Directives 67/548/EEC and 93/67/EEC. Since 1983, a total of over 5000 notifications have been submitted (for over 3300 substances).

During 2001, a total of 1045 dossiers (comprising 506 new notifications, and 539 updates) were distributed. Moreover, 316 final proposals for classification and labelling were distributed. Updates replace original notifications and therefore are not included in the notification statistics. These figures represent a further increase in notification submissions with respect to earlier years.

Annual notification statistics since 1983, analysed on a Member State basis, show that over half have been combined contributions from the UK and Germany. With regard to the origin of the substances, about half of the new commercial chemicals marketed in the EU during the year 2001 were foreign imports, principally from the USA.

Cumulative notification contributions for new chemicals per Member State (1983-2001)



THE AUTHORIZATION OF BIOCIDES

Biocides are chemical preparations containing one or more active substances that are intended to control harmful organisms (such as pest control). Biocidal products can pose risks to humans, animals and the environment in a variety of ways due to their intrinsic properties. In contrast with other chemical substances (existing and new substances), biocides are not allowed to be placed on the market without being authorised.

The Directive 98/8/EC concerning the placing of biocidal products on the market harmonizes the rules of such placement by introducing common data requirements for both active substances and biocidal products. This harmonisation intends to remove barriers of trade between Member States. During 2000, a first Review Regulation 1896/2000 (a follow-up to the Directive 98/8/EC) was agreed and addressed the review of 'existing active substances'. Preparatory discussions for the second review regulation took place in 2001.

In 2001, the ECB undertook the following tasks in order to prepare for the second phase of the review programme:

- The web page for biocides, <http://ecb.ei.jrc.it/biocides>, has been kept up-to-date, as a means to distribute information to third parties
- An enhanced version of IUCLID, adapted to biocides, was further discussed
- A guidance document on how to fill in the notification in IUCLID was prepared and posted on the web
- A document describing the "Procedure to check a Notification" has been completed
- Several IUCLID courses were successfully given to Biocides authorities and industry
- The ECB 'biocides team' participated in numerous events and conferences aiming at explaining the Biocides Directive 98/8/EC, the Review Regulation 1896/2000, and their consequences
- The various Technical Guidance Documents (TGDs) were further developed. One TGD on the first description of environmental emission scenarios for biocides was finalised and placed on the web.



THE INFORMATION EXCHANGE ON IMPORT AND EXPORT OF DANGEROUS SUBSTANCES

The ECB fulfils the duties of the Commission within the export notification process as laid down in Regulation 2455/92 by giving technical and scientific support for the implementation of the Regulation. The main issues of the Regulation are: to implement the EU export notification procedure; to make the voluntary UNEP/FAO Prior Informed Consent (PIC) procedure legally binding within the Community; and to use the same rules for classification, packaging and labelling outside the Community that apply in the internal market.

At the international level, a new regulation called the Rotterdam Convention was signed in September 1998, and is still in the process of ratification. The voluntary implementation of the Rotterdam Convention within the EU established the ECB as the central export notification authority on behalf of the Community. The European Database on **EX**port and **IM**port of certain dangerous chemicals (EDEXIM) was modified to meet the new requirements during the interim period until the Convention will be legally binding.

The ECB continues to develop the National Profile Homepage in collaboration with the United Nations Institute for Training and Research (UNITAR). This Internet site has information on the existing national legal, institutional, administrative and technical infrastructure related to the sound management of chemicals for over 80 countries. The Internet address is:

<http://www.unitar.org/cwm/nationalprofiles/index.htm>.

In addition, the ECB is actively supporting the development of several services within the INFOCAP project in the regime of the Intergovernmental Forum on Chemical Safety (IFCS).

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Hansen, B.G., Munn, S.J., Pakalin, S., Heidorn, C., Allanou, R., Pellegrini, G., Berthault, F., Scheer, S., De Bruijn, J., Vormann, K., Luotamo, M., Loonen, H., Vegro, S., Naughton, A., Anfossi, V., Praderio, L. (2001). European Union Risk Assessment Report. PCOC (4-Chloro-2-Methyl Phenol). CAS No. 1570-64-5- EINECS No. 216-381-3. EC. EUR 19757/EN. ISBN 92-894-0809-X.

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INSTITUTIONAL PROJECT

- Chemical products, risk assessment

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Support to Pharmaceutical Research

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Web Information resources

At IHCP site:

<http://ihcp.jrc.cec.eu.int/Activities/ACTPhar/ACTPhar.html>

Support to Pharmaceutical Research (SPR)

From the first European Community pharmaceutical directive (65/65/EEC), issued in 1965, to the present day, Community lawmakers have striven to ensure that medicinal products for human use help maintain a high level of protection for public health. Two landmark directives, 75/319/EEC and 75/320/EEC, sought to bring the benefits of innovative pharmaceuticals to patients throughout the European Community, by introducing a procedure for the mutual recognition, by Member States, of their respective national marketing authorisations. From 1985, many Community directives have been adopted with the aim of achieving a single, EU-wide market for pharmaceuticals.

In January 1995, a new European system for authorisation of medicinal products was established. The new European system offers two routes for authorising medicinal products (besides the purely national authorisations that are still available for medicinal products to be marketed within one Member State):

- A **“centralised” procedure**, with applications made directly to the European Agency for the Evaluation of Medicinal Products (commonly known as the European Medicines Evaluation Agency–EMEA) leading to the granting of a European marketing authorisation by the Commission. Use of this procedure is compulsory for products derived from biotechnology, and optional for other innovative medicinal products
- A **“mutual recognition” procedure**, which is applicable to the majority of conventional medicinal products. Applications are made to the Member States selected by the applicant and the procedure operates by mutual recognition of national marketing authorisations. Where this is not possible, the EMEA is called upon to prepare a binding arbitration.

The discharge of the regulatory and scientific tasks assigned to the European Commission, the EMEA and the national authorities in pharmaceuticals is a shared responsibility, which demands a high level of collaboration among the aforementioned actors.

Within this context, the SPR provides telematic support to EU pharmaceutical regulatory activity with the study and development of specialised information and communications systems and tools (including data models and application protocols) for electronic transmission, sharing, and management of information. The work is carried out in collaboration with DG Enterprise, the European Agency for the Evaluation of Medicinal Products (EMEA), National Agencies and the Pharmaceutical Industry.

The IHCP has developed a number of information/communication systems and applications in order to assist the access to information on medicinal products:

- The EudraNet services (supporting cooperation for the entire EU market and post-market control)
- The EudraTrack Mutual Recognition (EMR)
- Unified Tracking System: an extension of the EMR to support the marketing authorisations tracking of all medicinal products
- Medicine Information Network for Europe (MINE1): an interface for the dissemination of information on medicinal products.

The following sections will discuss in more detail the various IT systems and applications supported by SPR.

EUDRANET NETWORK SERVICES (ENN)

EudraNet (ENN) is a telecommunications network in the field of European human and veterinary pharmaceuticals offering ICT services. The objectives of EudraNet are:

- To enable electronic communication and sharing of information between the European Commission, the EMEA, and the national Competent Authorities (CAs) in pharmaceuticals
- To provide a gateway for the secure and managed communication over the Internet between European administrations and pharmaceutical companies
- To host and provide access to Community databases in pharmaceuticals
- To provide a collaborative group work environment.

More specifically, EudraNet provides network services, application services (common databases), and support services. It is a project under the responsibility of DG Enterprise carried out in collaboration with the IHCP/SPR, EMEA and national CAs.

The network consists of a backbone connecting dedicated lines of 32 organisations: the Commission, the EMEA and the national authorities responsible for human and veterinary medicines in the EU, Norway, and Iceland. Most local sites have their Internet and e-mail domains integrated within EudraNet. Electronic communication within EudraNet provides a 99.4% guarantee of service availability, which is regularly monitored.

In 2001, the JRC continued the experimentation with new inter-networking strategies by using the EudraNet 2 pilot project based on VPN technologies. Experimenting with the EudraNet’s co-operative virtual community by using VPN secure networking has exposed several is-

sues. The conclusion reached so far point out that a number of difficulties must be addressed in order to achieve a flexible and efficient secure networking by using a VPN approach.

Laying down security in the IP layer encounter significant problems especially at the level of firewall configuration. These problems become difficult to manage when a firewall is rented or is outsourced to another provider.

The study and evaluation of the adoption of a VPN version of EudraNet has focused our attention to an alternative more flexible approach, i.e. establishing a secure communication layer by using the transport layer (SSL and IVE). The study and evaluation of a EudraNet 2 based on secure communication by adopting cryptographic technique for the transport layer will be pursued in 2002.

In the second half of 2001, the project of the transfer of EudraNet to the EMEA (as decided by the European Commission and the national Agencies) has started. A complete reorganization of the current EudraNet has been designed. The implementation of this new architecture optimised for the EMEA take-over is in progress. Part of the SPR unit has been moved to London in order to ensure an efficient transfer to EMEA. In 2001, a strategy study on the future scenario of EudraNet has started, and will be completed in the first quarter of 2002.

EUDRATRACK MUTUAL RECOGNITION (EMR) SYSTEM

Within the context of EudraNet applications, EudraTrack (EMR) is a tracking system that permits the registration of procedures for marketing authorisation submitted through the mutual recognition process to Competent Authorities in the Member States of the European Union. Data items relative to mutual recognition procedures (full applications and variations) are introduced by the reference and concerned Member States in a shared database that is available under controlled access to the EudraNet users. It provides a global picture of the ongoing procedures and statistical reports of those already accomplished.

The EMR system is presently established as the official tool shared by Member States regulatory authorities (17 for human products, 17 for veterinary and two for vaccines and blood products). This system permits a first decision on the granting, suspension, withdrawal or amendment of a marketing licence to be made in one Member State (the "Reference") (RMS). A Member State submits the data using EMR to other "Concerned" Member States (CMS) as a basis for reaching mutual recognition at an EU level. EMR handles new applications, variations, renewals and extension of approvals; it stores a description of the product and records the actions of



Reference states and the comments and requirement of Concerned states throughout every stage of the authorization procedure.

In 2001, the EudraTrack activities have been reshaped in order to prepare the transfer of this system to a new operator in 2003. The EudraTrack infrastructure has been re-enforced and optimised. Also, action has been taken to validate the EudraTrack software in order to cope with software engineering standards before the start of transfer operations. Transfer is planned for the second half of 2002.

In addition, JRC has started a feasibility study in the framework of the Innovation and Technology Transfer programme to evaluate the concept of a JRC spin off (DigiTrack) capable to ensure the continuity of the EudraTrack project after the end of the FP 5.

In 2001, planning for future EudraTrack developments driven by legislation revision and technology evolution has been explored and it will be continued in 2002.

UNIFIED TRACKING SYSTEM (UTS)

The Unified Tracking System is an extension of the EudraTrack activities that provides a unified database of certified information to everyone. The UT system provides information not only on medicinal products that were authorised through the mutual recognition procedure (like EudraTrack), but also on medicinal products authorised through the centralised procedure. This telematic application for marketing authorization and post-marketing management of medicines combines the results of ATS and EMR in a single innovative system and represents a milestone towards the development of a common standard tracking system for the pharmaceuticals sector.

In 1999, the first UTS prototype was presented, allowing UTS users to trace the processes of authorization and evaluation of medicinal products. In 2000, a new classification into five levels of market authorization (MA) applications has been introduced (i.e. new active substance, initial application, full dossier, herbal and prescription). Moreover, the procedure header is now editable, allowing the update of contents of the following fields (e.g. CMSs, MA holder, Product name, Active substances, Pharmaceutical form, ATC code and RMS contact). In 2001, UTS has been further developed and tested by using product data derived from the EudraTrack Mutual Recognition (EMR) system.

Work done in the UTS context has been given as an input to the EuroPharm database project started in late 2000 within a cooperation of the national authorities (EuroPharm TIG). This action will continue in 2002 with the transfer of the JRC R&D results to the EMEA.

MEDICINE INFORMATION NETWORK FOR EUROPE (MINE1)

The Medicine Information Network for Europe (MINE1) is an interface application that provides tailored-based certified information on the safety of medicine authorised within the EU to specialised groups (patients, health professionals) (according to art. 7 of Council Conclusions of 29 June 2000 *see OJ C 218 dated 31 July 2000*). So far, a simple prototype has been developed that helps users browse the database of the EU authorised medicinal products. The data currently available consists of the medicinal products authorised through the centralised procedure until spring 2001, as well as the medicinal products authorised through the mutual recognition procedure between 1998 and spring 2001. In 2003, it is foreseen that the Euro PHARM database will be the EU reference database. Then it will be immediately operational because of its compatibility with the current database.

The main milestone for 2001 has been the development of a users community of patients and health professionals. In fact, to better understand the requirements of the public, SPR worked with the European Bureau of Consumer Unions (BEUC) since November 2000 in order to testing the prototype. A full-scale test took place in May 2001. The document summarizing the testing results has been finalised. In parallel, and in order to better understand the requirements of the health professionals, SPR has been working with the European Medical Association (EMA) since March 2001 in order to test the prototype and integrate the requirements of the medical profession. A workshop with general practitioners from all Member States and candidate countries took place in October 6th 2001 in order to collect their feedback.



Through continuous interactions with both BEUC and EMA, the request of consolidating the users community has emerged consistently. It is clear that the common communication tool (i.e. the MINE prototype) will evolve by integrating the adequate users interface to each of the four types of foreseen users: consumers or patients; medical or health professionals; pharmaceutical regulators; and decision makers (e.g. DG Enterprise, DG Health and Consumer Protection (SANCO), European Parliament, European Council, EMEA and national competent authorities). This will result in the sharing of the same database of information on medicinal products approved within the European Union and the same repository of documents that are elaborated during the MA processes of the medicinal products (e.g. summary of product characteristics (SPC) and product information leaflet (PIL)).

SPECIFIC EVENTS

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Pagliari, V. (2001). "EuroDatabase Model", presentation at the 3rd TIG meeting, June 8th 2001.

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INSTITUTIONAL PROJECT

- Telematic system for the EU pharmaceutical regulatory activity (ETOMEP)

OTHER ACTIVITY (THROUGH DG ENTERPRISE)

- EudraNet Services

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Web Information resources

At IHCP site:

<http://ihcp.jrc.cec.eu.int/Activities/ACTIndex.html>

At the BMS site:

<http://bms.jrc.cec.eu.int/>

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Biomedical Materials and Systems

Biomedical Materials and Systems (BMS)

The Biomedical Materials and System (BMS) Unit develops, validates and uses advanced processing techniques and test methodologies for the qualification of biocompatible materials, medical devices, and diagnostic systems including medical applications of nuclear technology. The above focus is based on the demands of an ageing European population and consumer insistence on tools for early diagnosis and better planning of therapies. In particular, diagnostic tools that lead to the minimization of surgery are needed for improving patient care and cost effectiveness of public health care systems.

More specifically, the BMS activities encompass the following main priorities:

- **Reliability of Biomedical Devices (REMEDI):** Activities in this priority area cover performance testing of biomedical devices in order to support the harmonization of testing methods for material release. This area also studies the performance of implant materials (orthopaedic and dental) and medical devices under clinically relevant conditions using a combination of advanced techniques (in support of Directive 93/42/EEC). It focuses on functional materials and systems, involving the development and characterization of biocompatible and bioactive surfaces in order to improve haemocompatibility of cardiovascular grafts, stents, catheters, and osteointegration of hip and knee replacement prostheses.
- **Minimally Invasive Medical Systems (MIMES):** Activities in this area apply nuclear and optical imaging techniques to medical diagnosis and therapy. This involves, amongst other activities, the contribution to the development of standards for the distribution of radiotracers, as well as the participation in relevant European Networks.

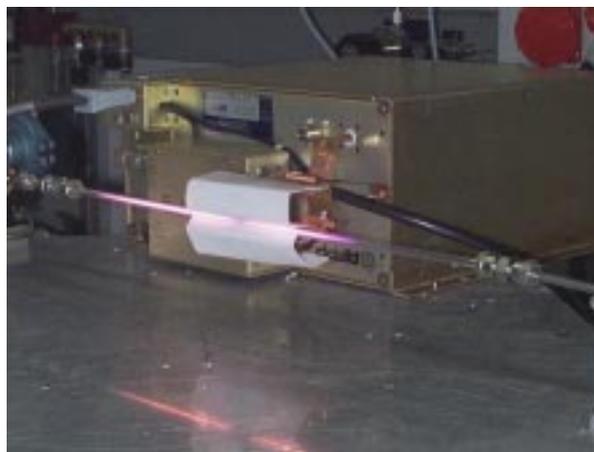
Both areas are of high relevance for maintaining quality health services, especially in view of demographic changes due to ageing of the population. The following sections will discuss in more detail the aforementioned priority areas and projects.

RELIABILITY OF BIOMEDICAL DEVICES (REMEDI)

Increased average life expectancy implies that critical body parts (e.g. bones, joints) will wear out and may need to be replaced. Biomedical devices or implants, engineered from biomaterials, and designed to perform specific functions now play a major role in replacing or improving the function of every major body system (skeletal, circulatory, nervous, etc.). These include dental implants and orthopaedic devices such as total knee and hip joint replacements, spinal implants or bone fixtures. From a regulatory point of view, acceptance of a wide range of medical devices at a European level requires the validation and harmonization of testing and characterization methods for the systems and the materials used. Providing Commission services (e.g., DG Enterprise, DG Health and Consumer Protection (SANCO)) with scientific and technical information related to the improvement of standards is necessary and is the rationale behind the project entitled "Reliability of Biomedical Devices" (REMEDI Project).

Biomaterials Processing and Coatings

Many of the problems related to medical implants and prosthetic devices are associated with the interface between biomaterials and biological tissues, bones, etc. The main issue is the behaviour of the host tissues with respect to an implant material and the ability of this material to fulfil its function in the *in vivo* environment. The study of interfacial phenomena provides guidance for the selection of materials and suggests that surface modifications may improve the host response to the biomaterial. Methods are being developed at the IHCP to study bio film formation on medical devices, prostheses, or implant surfaces and to define improved or new strategies for their safe use while ensuring adequate long term operation.



Prototype RF reactor for catheter treatment.

Carbon thin films have been deposited with a Plasma Assisted Physical Vapour Deposition (PAPVD) reactor. The system is based on the coupling of a microwave plasma source with two magnetron sources for carbon deposition. The geometry of the reactor allows the deposition of films on 3D shape substrates. Carbon films with a controllable diamond character have been deposited. Biocompatible diamond-like carbon (DLC) films are deposited on stainless steel, Ti-alloys used in stents, bone sutures and orthodontic appliances as protective coatings to avoid nickel migration.



Large Area Inductively Coupled Plasma Reactor.

CNx films have been deposited with PAPVD by using a carbon solid source coupled to a Distributed Electron Cyclotron Resonance (DECR) microwave plasma reactor. These types of film are also promising as hard coatings for prosthetic devices because of their diamond like character. Preliminary cellular studies, in collaboration with ECVAM, indicate that the cells adhered well to the coated support, showing the typical morphology of fibroblast growth in monolayer.

A biocompatible surface can be obtained by covalent immobilisation of proteins, such as heparin, on the medical devices. One method is to graft aldehyde, carboxylic or epoxy moieties on the surface and to covalently bond the antibodies through their amine functions. BMS has deposited a functional film by plasma polymerisation of acrylic acid vapour using an inductive plasma source. X-ray Photoelectron Spectroscopy (XPS) and Infrared analyses of the coatings show that acrylic functionalities can be maintained during deposition and a thin film of 200 to 1000 nm can be deposited with strong carboxylic character. Wetting studies indicate the possibility of tailoring surface physical properties (hydrophobic-hydrophylic surfaces) by adjusting the plasma parameters.

Another activity initiated during 2001 is related to the use of plasma sources for sterilization and cleaning purposes. This is related to the project STERIPLAS, in which

plasma processing is used for pyrogen destruction in medical devices and polymer treatment for pharmaceutical packaging. The radiofrequency and microwave sources have been tested for different gas mixtures (O_2/Ar , H_2/Ar , O_2/H_2 and N_2/O_2). Several *in situ* diagnostic techniques, Optical Emission Spectroscopy (OES), Mass Spectrometry and Electrostatic Probe (Langmuir probe) have been applied to identify the species present in the discharge. Optimised conditions for sterilization and cleaning of surfaces have been identified.

Performance Testing

Following the suggestion of the 1999 Audit Report to establish with ECVAM a reference and consulting body for European biomaterials testing, collaboration with ECVAM was further intensified. In 2001, the European Commission accepted a joint BMS/ECVAM proposal for a Marie Curie Training Site on "Research training in biomaterials testing using radiotracers" (BIORAD). A study for clean room laboratories in the cyclotron-controlled area was carried out. There are also ongoing projects concerning the health effects of wear debris and metal compounds.

Wear Release Methodologies for Orthopedic Implants

A 12-station screening wear test facility based on a novel design was constructed and became operational in 2001. Three different types of multi-directional screening wear test facilities are available to develop new screening wear test methods to replace the former ASTM F732 standard for evaluating medical grade polyethylene. This is highly relevant considering the clinical use of cross-linked polyethylene, a material expected to be very wear resistant, although subject to alerts by medical device agencies. The work was dedicated in large part to these new materials, including oxidation during storage and long-term clinical use.

After the successful introduction of Thin Layer Activation (TLA) for very sensitive wear monitoring of polymers (as suggested in ISO TR9326) in collaboration with the cyclotron facilities of CNRS Orleans France, TLA was used for the first time on cross-linked polyethylene. The method demonstrated its high sensitivity and accuracy compared to conventional techniques. With regard to the clinical problem of spallation of wear resistant films and coatings, experimental procedures were assessed. This activity is exploited in the frame of competitive activities (SCAs) on alumina layers and functionally graded materials and is related to the surface modification activities within IHCP. To assess the cellular response of wear debris, procedures for isolation of wear particles from biological solutions after testing were developed in collaboration with ECVAM. Further work to test these particles for their long-term health effects is carried out with ECVAM.

Advanced Release Testing Methods for Medical Devices

In view of the increasing number of clinical cases reporting adverse effects due to material release from medical implants there exists a need for advanced release testing methods. This activity is linked to related ECVAM activities. It is relevant not only to the Medical Device Directive 93/42/EEC, but also to Directive 94/27/EC and to the new Preparations Directive 99/45/EC. The latter formed the subject of an ECVAM workshop in February 2001 that identified the critical issues in test methods and served to focus the research efforts on test method development.

Material release from orthodontic materials is of increasing concern. The situation is rather complex in view of the wide range of materials (more than 5000 in Europe) used in orthodontic applications, the varying clinical conditions during use and the absence of reference test procedures. The activity on the release from dental systems involved the use of different test conditions and test solutions. The use of radiotracers in these studies proved to be very useful, indicating the instability of various solutions during long-term testing. The growing use of different components in a single implant, with possible significant influence on local release rates, motivated the use of radiotracers to measure the local release rates. The study of the effect of proteins on the release of implants is also being carried out in support of the improvement of ISO 10993 (Biological evaluation of medical devices) part 15. Since fretting appears to be of increasing clinical relevance, relevant test methods are required. This research is supported through a Marie Curie individual fellowship.

Databases and Implant Registers

This work package was included in 2001 in view of a growing interest at a European level to set up databases on medical devices and adverse reactions to biomaterials. Following preliminary consultations held with DG Health and Consumer Protection (SANCO), a proposal for a concerted action on Harmonisation of European Adverse Reactions Databases (HEARD) was submitted to the SANCO Public Health Programme.

MINIMALLY INVASIVE MEDICAL SYSTEMS (MIMES)

Minimally invasive systems are being developed based on radioisotope and optical methods. Both applications are becoming increasingly important for improved systems for early and more precise diagnoses and better therapeutic treatments, especially for cancer patients.

Radioisotope production

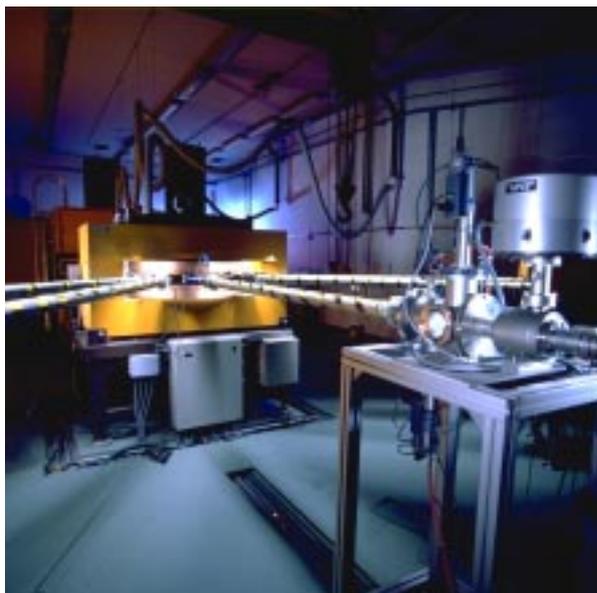
The IHCP operates a cyclotron, which allows the production of a vast variety of radioisotopes. Due to its technical characteristics, it is best suited for research into the production technology of radioisotopes for new medical applications. Radioisotopes can be used for labelling all kinds of molecules as biomedical radiotracers. The nuclide-specific radiation emitted from such radiotracers makes it possible to detect, localise and follow their movement. Such isotopic labelling allows the study of the functioning of the living body, from individual cells to the entire organism.

Radioisotope applications in nuclear medicine cover both diagnosis and therapy. They allow a functional imaging of body tissue and its response e.g. to medication. Radiotracer studies help to understand the working of the brain, to detect cardiac disorder, or to track down cancerous metastases, etc.

Positron Emission Tomography (PET), the most advanced nuclear imaging technique, is now becoming a tool for diagnosis of cancer by use of short-lived, positron-emitting isotopes, which can only be produced by accelerators such as cyclotrons. The enormous potential of PET in clinical practice and medical research as well as emerging radionuclide therapies for dispersed and inoperable cancers will lead to a strongly increasing demand for radiopharmaceuticals. An increased cost-effectiveness in the management of cancer patients and the medical and economic advantages of less invasive treatment of several groups of diseases will promote this development. IHCP responds to these demands by collaboration with industry and networking with other research groups.

The establishment of a radiopharmaceutical laboratory for the production of [^{18}F] FDG (2-deoxy-2[^{18}F]-fluoro-D-glucose) has made considerable progress in 2001. In collaboration with an industrial partner, extensive testing of the production process including quality control has been carried out. The laboratories are being prepared for operation under in compliance with GMP (Good Manufacturing Practice). Commercial production aims at acquiring practical knowledge in the field of quality control at all stages of the production process and on the technical issues of distribution and delivery of short-lived radioisotopes to hospitals and research organisations. This knowledge is of strategic importance, given the lack of Europe-wide regulations for the production and distribution of PET radiopharmaceuticals, which hinders the equal access of European citizen to the best possible health care services.

The JRC-Cyclotron has acquired a significant experience on radioisotopes production through the previous ^{123}I radioisotope production, which has been carried out twice a week until November 2001.



IHCP Cyclotron.

Presently JRC-Cyclotron is also involved in initiating a ^{64}Cu production via another way of activation route in collaboration with Milan University. ^{64}Cu radioisotope is both β^+ and β^- therefore it can be used simultaneously for PET diagnosis and therapy of cancers.

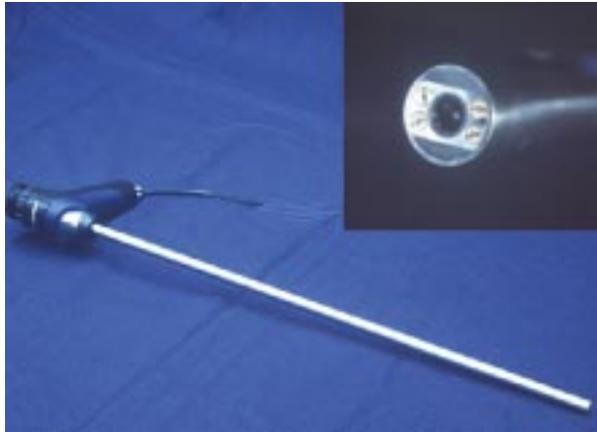
Optical Methods

In recent years there has been an increasing interest in applying optical techniques to medical diagnosis and therapy. This interest has been stimulated by modern laser, fibre optic, and signal processing technology, which allows systems to be built that can easily be operated in clinical environments. The BMS Unit is particularly interested in developing innovative systems for minimally invasive diagnostics and patient monitoring. There is also a strong interest in applying optical techniques to biomechanical studies in order to improve treatment strategies for musculo-skeletal disorders such as osteoporosis. Depending on the application, optical techniques may offer several advantages over more conventional diagnostic methods, in that they are minimally invasive, radiation free, low cost, reliable, and may even be used actively during surgical procedures to aid and improve treatment. The year 2001 saw the relocation of the optics group to a new suite of laboratories, and focusing of the activities in the biomedical field.

Several optical systems for patient monitoring and diagnosis have now been patented. Further development and testing is in progress before moving on to clinical trials of these systems. Sensors for *in-vivo* monitoring of temperature and pressure are based on modern fibre optic technology. Temperature measurement is based on Bragg gratings whereby a periodic variation of the refractive index of the core of an optical fibre is induced through exposure to a UV interference pattern set up by an appropriate optical system. The BMS has one of only a few such systems in Europe, and furthermore has developed numerical routines for designing custom-made Bragg gratings. Pressure measurement is based on the use of an un-encapsulated, looped and tapered, fibre-optic coupler that is inserted into a miniature cylinder with an end diaphragm. Changes in external pressure induce changes in the coupling ratio, and the resulting intensity changes can thus be calibrated in terms of pressure.

Fluorescence-based analysis of tissue holds the potential for minimally invasive detection of certain types of cancer. This may be based on auto-fluorescence or deliberate introduction of fluorophores into the tissue. The most common detection method is via fluorescence intensity, and the BMS optics group has developed and patented a novel endoscopic system for such measurements. A more advanced detection method is based on mapping fluorescence lifetimes. This requires specialised optical and signal processing systems, and initial work has started in this area. Another area where optical methods could have an impact in the future is in tumour detection using infrared photon migration systems. The main challenge in this area is in developing inverse methods for reconstructing tissue properties

from measured photon intensity variations. A collaborative effort has led to the development of a differential Monte Carlo code that could be of great significance in this respect. The process of code validation is now being initiated.

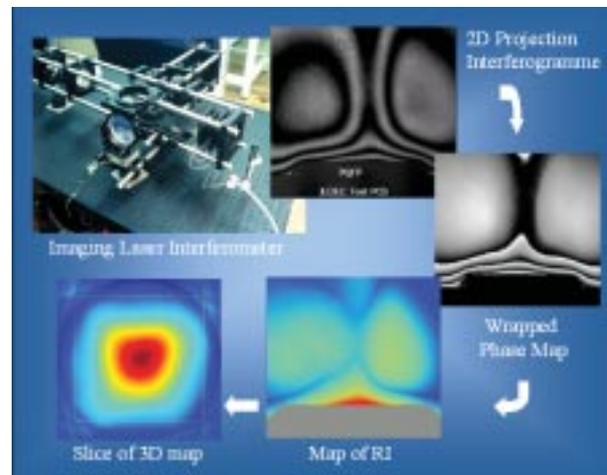


Prototype medical endoscope system with integrated optical fibre sensors for minimally invasive in vivo diagnostics.

A significant effort has been made in 2001 to develop our understanding of the biomechanics of bone and bone implants, as well as diagnostic techniques for diseases such as osteoporosis. This is a highly appropriate activity for the BMS at the start of the “Bone and Joint Decade” – a global campaign announced in 2000 by the World Health Organisation (and endorsed by the UN), to improve the quality of life for people with musculoskeletal disorders. Tools have been developed for both computational and experimental biomechanics, and effort will be focused on one of the principal causes of failure of hip prostheses – stem migration and loosening. There

may be several reasons for this, and one of the reasons for early failure of cemented prostheses is the presence of high residual stresses in the cement mantle due to the curing process. In order to develop more reliable implants it is necessary to expand our understanding of the curing process and how cement shrinkage contributes to stresses within the PMMA and at the interfaces. Advanced optical methods are being applied to the quantification of these stresses in simple test geometries with the aim of building up and validating full 3D finite element models of implanted femurs.

The IHCP is co-chairing the working group 7 “Health Technology Assessment” and working group 8 “Education, Training, Public Education and Awareness” of the EMIR (European network for Medical Radio-Isotope and Beam Research) network.



Laser interferometer system for 3D functional imaging - reconstruction of whole field distribution of refractive index (RI) of fluids and tissue structures.

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INSTITUTIONAL PROJECTS

- Reliability of Biomedical Devices (REMED)
- Minimally Invasive Medical Systems (MIMES)

SOME SHARED COST ACTIONS

- STERIPLAS, LAPLADIS, MEDPHOT, BIOGRAD, ALUSI

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Contributing to the European Research Area

In January 2000, the European Commission proposed the creation of a **European Research Area** (COM (2000) 6). The main objective was to enhance the efficiency and innovative impact of Europe's research effort through better integration and co-ordination of research activities at a European level.

The IHCP has contributed to the implementation of a European Research Area (ERA) through scientific networking, the promotion of research training and mobility, and support to EU enlargement.

NETWORKS

The IHCP sought to network with EU Member States, Accession Countries, and Association countries with a view of co-ordinating research and exchange scientific and technical information:

- European Network of GMO Laboratories (ENGL)
- European Food Safety Network (EFSN)
- European Food Allergy Network
- European Network on Food and Nutrition to prepare projects for the European Research Area (ERA)
- European thematic network on Optical Methods for Medical Diagnosis and Monitoring of Diseases (MEDPHOT)
- European thematic network on Innovative Plasma Technology for Societal Needs (PLASMATECH).

RESEARCH TRAINING AND MOBILITY

The ERA promotes greater training and mobility of young and senior researchers as they play an important role in the collaboration and networking of European research. Within this context, the IHCP hosted 55 collaborative staff including trainees, grant-holders (post-graduate and post-doc), visiting scientists, and seconded national experts.

SUPPORT TO EU ENLARGEMENT

The IHCP supports the adoption and implementation of EU legislation (*acquis communautaire*) in the Accession Countries through specialised enlargement activities (training and workshops):

- FPU participated in two TAIEX (Technical Assistance Information Exchange Office) meetings (on GMOs, and food contaminants, including food contact materials) and in specific food control conferences organised by EU accession countries (in Slovakia, and the Czech Republic).
- FPU organised a meeting in Ispra on food safety and quality for the implementation of EU Food Legislation with a focus on needs for scientific and technical support. This workshop was attended by about 50 scientists from all EU Accession Countries.
- ECVAM sponsored a conference on alternatives to animal experimentation, which was held in Prague and attended by about 100 scientists from Croatia, the Czech Republic, Germany and Slovakia.
- A 2-day joint training course on the *Validation of alternative methods for regulatory toxicity testing* was organised by ECVAM and the European Society of Toxicology for scientists from Accession Countries and the EU Member States. Out of a total of 17 participants, 13 were from Bulgaria, Croatia, the Czech Republic, Estonia, Lithuania, Slovakia, and Slovenia.
- BMS is a partner in an INTAS (International Association for the Promotion of Co-operation with Scientists from the New Independent States of the former Soviet Union) project in the field of plasma surface modification techniques for biomedical materials.

IHCP Performance Indicators–2001

Shared Cost Actions

- SCA started in 2001: 13 (included in the ongoing 19)
- Total ongoing SCA in 2001: 19

Publications

- Articles: 75
- Technical EUR Reports: 19
- Conferences: 125
- Special Publications: 27
- *TOTAL: 246*

Prizes/Awards

- JRC-Innovation Project 2001 Award: Mycotoxins in food and animal feed.
- JRC Young Scientist Prize 2001: A. Worth was awarded one of three JRC Young Scientist prizes for 2001, for his contribution to the scientific basis of toxicological hazard prediction (the development and evaluation of mathematical models for chemical toxicity based on physicochemical or *in vitro* data).
- Best poster presentation: Genetically engineered embryonic stem cells have been established in ECVAM laboratories providing information on chemical effects on the endodermal differentiation, an endpoint to be used for the assessment of the embryotoxic potential of xenobiotics. The data resulted in 2001 in an award for the best poster presentation on the MEGAT Congress in Linz/Austria.
- T. Meziani, P. Colpo, and F. Rossi, "Design of a Magnetic Pole Enhanced Inductively Coupled Plasma Source". Awarded as best oral contribution from a PhD student from the French Vacuum Society.
- The laboratories on Product Release Testing for Exposure Assessment were selected to host a Marie Curie Training Site on testing of biomaterials using radio-tracers.

Nominations

- M.F. Stroosnijder was nominated chairman of the VAMAS (G8 Versailles Project on Advanced Materials and Standards) Working Area 7 Biomaterials.
- D.G. Rickerby was nominated as visiting professor at the INRS, University of Quebec.

Patents (received by IHCP)

Numbers

- In 2001: 5
- Total since 1998: 14+5=19

Description of patents received in 2001

- Portable sampling lance that can be used to sample agricultural goods for contaminants, such as mycotoxins in a simple, non-destructive way (J. Stroka).
- Process chamber for plasma processing and apparatus employing said plasma chamber. Application number EP 98400888.8, Ref. JRC 2538.
- Plasma processing apparatus with an electrically conductive wall. Application number 99 402 845.4, Ref JRC: 2623.
- Method and apparatus to produce large inductive plasma for plasma processing. Application number: EP 98401199.9. Dos: 2560.
- Uniform gas distribution in large area plasma source. Application number: 99 402 374.5. Dos 2632.

Training

- Three ECB training courses on IUCLID and EU risk assessment procedures.
- A 2-day joint training course on the *Validation of alternative methods for regulatory toxicity testing* was organised by ECVAM and the European Society of Toxicology for scientists of the Accession Countries and EU Member States.

Competitive Activities (2001) – Examples*

FOOD SAFETY

STRATFEED

Aim:

Development and validation of new methodologies for the detection and quantification of illegal addition of mammalian tissues in feedingstuffs.

Partners:

- National Agricultural Research Centre (B)
- State Institute for Quality Control of Agricultural Products (NL)
- Italian National Institute of Health – ISS (I)
- Scottish Agricultural College SAC (UK)
- Laboratory of the Autonomous Government of Catalonia LAGC (E)
- State Official Laboratory ROLT (E)
- Agronomy Science University – FUSAGx (B)
- School of Agriculture and Forestry Engineering of University of Córdoba (E)
- Maasweide Laboratory, Nutreco (NL)

SIMBAG-FEED

Aim:

Method development and validation for the detection of specific veterinary drugs in feed.

Partners:

- State Institute for Quality Control of Agricultural Products – RIKILT (NL)
- Staatliche Landwirtschaftliche Untersuchungs- und Forschungsanstalt – LUFA Augustenberg (D)
- Danish Plant Directorate (DK)
- IZ LUFA ITL – Kiel (D)
- Direction Générale de la Concurrence, de la Consommation et de la Répression des Fraudes – DGCCRF (F)
- Bavarian Department for Nutrition – LfE München (D)
- Laboratório Nacional Investigaçao Veterenaria (PT)
- Instituto Superiore Sanità (I)
- National Veterinary Institute – Uppsala (S)

ADVANCED ALTERNATIVE TESTING METHODS

DRUGS AND SAFETY

Project Name: FP5 Project “Comparison and Validation of Novel Pyrogen Tests based on the Human Fever Reaction”.

Aim:

To develop, evaluate and validate methods for the identification of pyrogens (fever inducing contaminants) in injectable drugs to replace the rabbit pyrogen test and the Limulus assay, both part of the European Pharmacopoeia requirements.

Partners:

- Steinbeis Transfer Centre For *In Vitro* Pharmacology and Toxicology at the University of Konstanz (G), NIBSC (UK), PEI (G), RIVM (NL), University of Innsbruck (A), University of Bern (CH), Novartis (CH), NIPH (NO), European Pharmacopoeia (F)

* IHCP participation in shared-cost actions with other successful consortia.

FOOD QUALITY

GLYCEROL

Aim:

Assessment and validation of methods to ascertain the illegal addition of glucerol to wine.

Partners:

- Eurofins (F), Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin (D), Central Science Laboratories–Ministry of Agriculture, Fisheries, and Food (CSL) (UK), Istituto Agrario di San Michele all'Adige (I)

MEDEO

Aim:

Investigation of state-of-the-art-methods and analytical techniques to detect the adulteration of olive oil with hazelnut oil.

Partners:

- International Olive Oil Council (based in Spain)
- Instituto de la Graca–CSIC.IGS (E), Instituto de las Fermentaciones Industriales–CSIC-IFI, CSL (UK), National Hellenic Research Foundation (GR), Dep. Qualité Produits Agricoles (B), Istituto Sperimentale Elaiotecnica (I), Stazione Sperimentale Oli e Grassi (I), Istituto Chimica Nucleare–CNR (I)
- Eurofins (F), Andoleum (S), University Agricultural Sciences–Vienna (A), Univ. Catholique Louvain (B), Univ. Complutense Madrid (E)

WINE DB

(starts in 2002)

Aim:

Establishing a wine data bank for analytical parameters for wines from third countries.

Partners:

- Bundesinstitut für gesundheitlichen Verbraucherschutz und Veterinärmedizin (D), Department for Environment, Food and Rural Affairs (UK), Eurofins (F), Vrije Universiteit (B), Ministry of Finance (CZ), Agronomical University and of Veterinary Medicine 'Ion Ionescu de la Brad' (RO), National Institute for Wine Qualification (HU), Croatian Institute of Viticulture and Enology (CR)

COFAWS

Aim:

Confirmation of the origin of farmed and wild salmon and other fish.

Partners:

- Eurofins (F), Université de Nantes (F), North Atlantic Fisheries College (UK), SINTEF Fisheries and Aquaculture (SINTEFA) (NOR)

GMO

ENTRANSFOOD

Aim:

Identification of key issues of the safety evaluation of genetically modified food crops.

Partners:

- RIKILT (NL), VBF (DK), UDUR.DBS (UK), CEA-Cad (F) EC JRC IHCP (I), IFA-Tulln (A), IFR (UK), RRI (UK), UNILEVER (UK), ISS (I), CEA-SPI (F), IEM (S), BIBRA (UK), TUM (D), Metapontum (I), LEI (NL), TNO (NL), KERKA (EL), SCRI (UK), RKI (D), ILSI (B), BgVV (D), Agre Vo (UK), IFT (D), EC JRC IRMM (B), BEUC (B), UKU (FIN), AHOLD (NL), Monsanto (B), Nestlé (CH), NVI (N)

QPCRGMOFOOD

Aim:

Development of reliable and transformation-event-specific tests for qualitative and quantitative detection of genetic modifications in food.

Partners:

- National Vet Inst (N), MATFORSK (N), INRA (F), DvP-CLO (B), LGC (UK), Gene-Scan (D), TERPAL-Danone (F), Unilever (NL), Bio-GEVES (F), DGCCRF (F), IFR (UK), CSIC (E)

BIOMED

STERIPLAS

Aim:

Study and validation of an advance plasma sterilisation process.

Partners:

- ARJO WIGGINS (F), R BOSCH GmbH (D), METAL PROCESS (F), BIOMATECH S.A. (F), C.I.R.M. (I)

LAPLADIS

Aim:

Large Area Plasma Etching Process for Display Applications.

Partners:

- FIAT (I), THOMSOM (F), FHR, EUROINKS

ALUSI

Aim:

Development of alumina forming ODS ferritic superalloys as new biomaterials for surgical implants.

Partners:

- Consejo Superior de Investigaciones Científicas (CSIC.CNIM) (SP), Asociación Instituto de Biomecánica de Valencia (SP), Istituto Ortopedico Rizzoli (I), Technische Universität Clausthal (D), Surgical (SP), Metallwerk Plansee GmbH (G)

BIOGRAD

Aim:

Increasing the performance of total hip replacement prostheses through high functionally graded material.

Partners:

- Lima Lto (I), Ceramtec (D), IMT Bodycote (UK)
- University Leuven (B), Helsinki University Technology (FI)

MEDPHOT

Aim:

Use of optical Methods for Medical Diagnosis and monitoring of diseases.

Partners:

- ISIS OPTRONICS GmbH (D), R. Wolf GmbH, STORZ (D)
- FORTH-ISEL (GR), PTB-National Metrology Institute of Germany, Lund Laser Centre (D)
- ILM-University of Ulm, Robert-Rossle Hospital-Berlin, Humboldt University, MLL-University, Lubeck (F), Storz (D)
- University L'Aquila (I), Uni Paris XIII (F), U Twente (NL)
- AMC, Laser Centre (NL), Politecnico di Milano-POLIMI (I), Academisch Ziekenhuis Rotterdam (NL), ICSTM- Imperial College (UK)

European Commission

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JRC and the IHCP

<http://www.jrc.org/>

The Joint Research Centre (JRC) is a Directorate General (DG) of the European Commission. It has its headquarters in Brussels and seven institutes located in five separate sites:

- Institute for Reference Materials and Measurements (IRMM) — Geel, Belgium
- Institute for Transuranium Elements (ITU) — Karlsruhe, Germany
- Institute for Energy (IE) — Petten, The Netherlands
- Institute for Prospective Technological Studies (IPTS) — Seville, Spain

The largest site is located in Ispra, Italy, hosting three institutes:

- Institute for Health and Consumer Protection (IHCP)
- Institute for Environment and Sustainability (IES)
- Institute for the Protection and Security of the Citizen (IPSC)



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