# Institute for Health and Consumer Protection

# ANNUAL REPORT

EUROPEAN COMMISSION
JOINT RESEARCH CENTRE

Report EUR 19909 EN

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joint research centre
EUROPEAN COMMISSION

## Mission

*The mission of the IHCP is to support EU policies for health and consumer protection. The Institute carries out research to improve the understanding of the hazards, exposure and risks posed by food contaminants, drugs, chemicals, products, services and systems and to develop, validate and apply advanced methods and strategies of high scientific quality.*


**European Commission**
Joint Research Centre (DG JRC)
Institute for Health, and Consumer Protection (IHCP)

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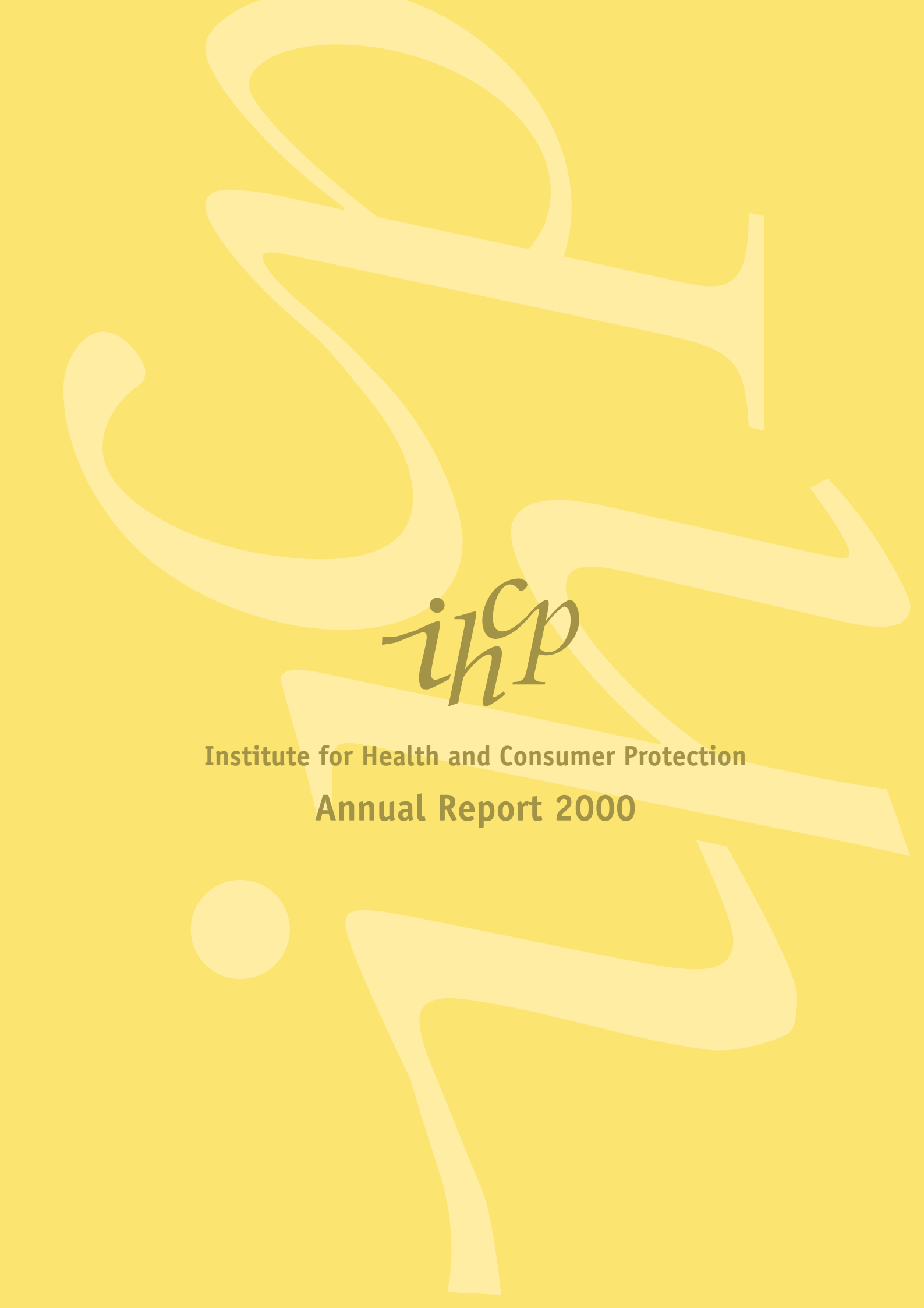
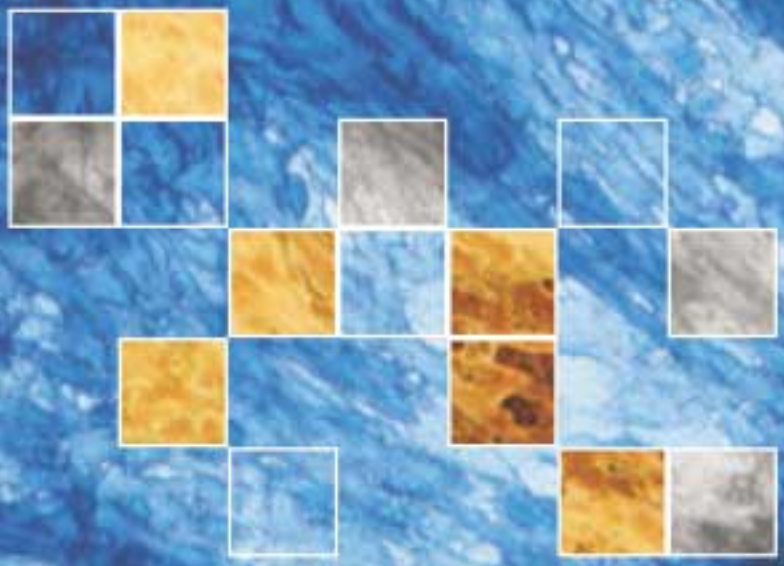
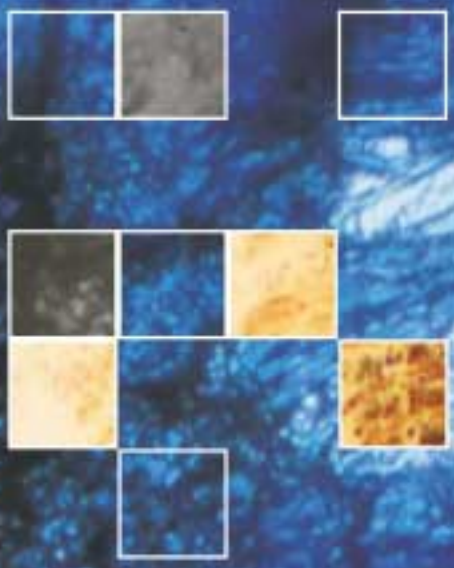


Institute for Health and Consumer Protection

# Annual Report 2000



Institute for Health and Consumer Protection



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# Foreword

It has been an honour and a challenge to take up my duties as first Director of the Institute for Health and Consumer Protection on 01/03/2000. Now, after one year, I am proud and happy to welcome the issue of its report for the year 2000. The year just passed has been a though one, dense of events but, more important, full of success stories, as detailed in the report.

Rapid developments in life sciences, the Commission's legislative programme and the New Policy on Chemicals have strongly influenced and accelerated the focusing and prioritisation of the Institute activities. The areas less relevant to th Institute's mission have been discontinued or transferred. Others like GMOS related research, have on the contrary expanded in response to the fast changing requirements for scientific support to Community policy making.

The strengthening of the interactive dialogue with DGs, the enlargement of its networking base and establishment as a major training provider, have rendered the IHCP the reference point for issues related to food and to the chemicals policy in Europe.

The IHCP has been central to the development of the JRC competence pillar on "Food, Chemical Products and Health". Through the Institute, the JRC is co-ordinating the European Network of GMO laboratories, has achieved a prominent position in the European Food Authority, under establishment and is central to the implementation of the White Paper on Chemicals in Europe, for all aspects ranging from pure regulatory ones to the development of alternative methods. Moreover, other activities (e.g. support to pharmaceutical regulation, biomedical) have been highly recognised by our partners.

All these achievements were made possible with high commitment from all the staff, which I wholeheartedly thank for their performance, sense of responsibility and personal participation in the Institute's life.

The future requires continuous engagement to consolidate some areas and to keep our deliverables at the highest standards. I am sure that with such premises our impact in the European area will continuously increase and further progress can be reported a year from now.

**Barry McSweeney**
IHCP Director

Director
**B. McSweeney**

Management Support
**G.P. Tartaglia**

Food Products
**E. Anklam**

Validation of Biomedical Testing Methods
**M. Balls**

Toxicology and Assessment of Chemical Substances
**G. Vollmer**

Pharmaceutical Regulatory Activities
**F. Argentesi**

Biocompatible Materials and Systems
**H.Stamm**

# Executive Summary

The year 2000 was the second year of operation of the JRC's newest Institute. The Institute's first Director, Barry Mc Sweeney, was appointed on 1 March 2000; prior to this, Herbert J. Allgeier, Director-General of the JRC, acted as Director of the IHCP. The IHCP has continued to progress and undergo a natural evolution in its working areas. The appointment of the Director accelerated the focusing and prioritization of IHCP activities. The prioritisation, mainly based on customer demand, has lead to the transfer of some activities (i.e. on electronic commerce), to the discontinuation of the project "COCO" on release from consumer products, to the streamlining of projects on medical devices and to the expansion of other activities (e.g. GMO).

## Strategy

Strategic plans were based on elements such as the Commissions legislative programme, the New Policy on Chemicals, the White Paper on Food Safety and rapid developments in life sciences. Driven by principles such as the reinforcement of the dialogue with DGs and other Commission services and the European Parliament to better focus on customer demand, the enlargement of its networking base and the establishment of the Institute as a training reference point, the IHCP has internally become central to the development of the JRC competence pillar on "Food, Chemical Products and Health", in collaboration with other Institutes, i.e. IRMM and IPTS. Externally it has become the reference point for issues related to food and chemicals products.

## Evolution

Due to growing consumer concern, there has been persistent demand for work related to food safety and quality, leading to an expansion of activities in this area in the context of the Commission White Paper on Food Safety and the proposal for establishing a European Food Authority. IHCP is leading a working group during the planning phase of the food authority in order to avoid duplication of activities between the authority and the JRC will be avoided.

The IHCP will strengthen its involvement in fields related to the authenticity and quality of organic foods. A detailed review of BEVABS work will take place in 2001. With regard to food safety, the evolution of the safety of feeding stuff will be followed. Monitoring will continue on polychlorinated biphenyls, phthalates and other plasticizers in childcare articles. There will be openings in new fields such as neutraceuticals and proteomics.

The GMO area received a tremendous boost in the year 2000, under the impulse of the Commission legislative programme. New staff are being taken on and the construction of new laboratories is under way. IHCP is increasing its activities in the area of certified reference materials and is setting up a molecular register for the identification of GMOs. Through IHCP, the JRC will coordinate the recently established international network of GMO laboratories, reference example in the context of the European research Area.

The forthcoming White Paper on safety of chemicals includes the IHCP as one of the main participants taking part in the formulation and further implementation of the chemicals policy. IHCP can be expected to provide further impetus to the future development of the activities of both ECVAM (European Centre for the Validation of Alternative Methods) and ECB (European Chemicals Bureau), which continue in their work related to the safety of chemicals and chemical products.

The IHCP also continued its work on telematics, in relation to regulation of pharmaceuticals. Present support given to the European Medicine Evaluation Agency (EMEA) is being strengthened, in addition to the activity on the development of the Medicine Information Network for Europe (MINE). Biomedical research activities have been re-oriented and concentrated on the reliability of medical devices, including implants, and progressive interdisciplinary work is now being carried out on replacement hips, knees and cardiac stents. Current strategy and future evolution in this area are based on the requirements of an ageing European population and consumer demand for better medical devices and early diagnostic systems.

A key activity has been the impulse given to the development of networking. Beside the GMOs network mentioned above, a major network on food safety has been established. Moreover, the number of collaborations in the field of alternative methods has continued to increase, as well as the number of bi-lateral collaborations in all Institute's areas.

## Food Products Unit (FPU)

### Safety and Quality of Food

The analysis of food products and consumer goods is geared to responding adequately and independently to consumer concerns regarding food safety and quality, and providing high-level technical support for the implementation of EU policies in the field of food and related items.

Evaluation of methods for the assessment of heat treatment of animal meat and bone meal: The IHCP is coordinating the 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.

Central nervous tissue (CNT) in meat products: a new activity started in 2000 for the determination of CNT (such as brain and spinal cord) in meat products, as specified risk material (SRM). These investigations respond to the need to assess the risk of human exposure to transmissible spongiform encephalopathies (TSE).

Polychlorinated biphenyls (PCBs): two methods for the rapid analysis of PCBs have been in-house validated and are accepted for use in routine analysis: the gas chromatography/mass spectrometry (GC/MS) method based on a simplified clean up procedure and an immunoassay method.

European Office for Wine, Alcohol and Spirit Drinks (BEVABS): data on the 1999 vintage have been measured (nuclear magnetic resonance). Development of the database on authentic European wines continued and the software was updated. Moreover, work on the development and validation for carbon-13 measurements is progressing.

Vegetable fats: A method for the detection of cocoa butter equivalents (CBEs) in cocoa butter (CB) has been developed.

Natural toxicants: A simple, environmentally friendly method based on thin layer chromatography (TLC) for the quantification of aflatoxins in food and animal feed was developed and validated. In the frame of support to CEN TC 275/WG 5, a suitable analytical method for the determination of aflatoxin B1 in baby food was delivered at the meeting held in Rotterdam in February 2000.

Food Contact Materials: A study on the effects of the composition of can coatings on migration of ether degradation products (BADGE, BFDGE) was completed, as part of monitoring contaminants from food packaging (i.e. can coatings, baby bottles, baby food jars sealant etc.). Comparison of methods for the migration of Bisphenol A in baby bottles was also completed. Validation of two methodologies to test the migration of certain plasticizers from toys and childcare articles was carried out.

**GMOs**

The GMO project addresses challenges related to biotechnology regulatory actions for environmental development, consumer protection and technological/industrial development, provides assistance to the Commission, to the relevant competent authorities and to European and national expert Committees in their work on the implementation of the Biotechnology Directives. Through the IHCP, the JRC is co-ordinating the recently established international network of GMO laboratories.

A notification system called SNIF has been developed as specific scientific and technical support offered to DG Environment with respect to the implementation of Directive 90/219/EEC on the contained use of genetically modified micro-organisms and Directive 90/220/EEC on the deliberate release into the environment of GMO, including all amendments and technical adaptations.

Reference materials containing GMOs (produced by IRMM) have been extensively analysed by direct PCR and by nested PCR, with the application of a large variety of PCR primers. This enabled new production protocols to be developed and collaboration to begin on the production of new types of materials. Three training courses were organized in collaboration with the World Health Organization. Applications for an additional ten courses are being processed.

## European Chemicals Bureau (ECB)

The European Chemicals Bureau provides scientific and technical support in the conception, development, implementation and monitoring of EU policies on dangerous chemicals. It represents the focal point for collecting information on new and existing chemicals and the assessment of risks to workers, consumers and the environment.

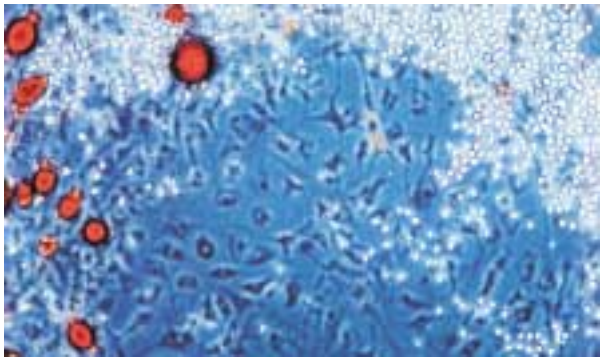
ECB has introduced 11 new and revised testing methods into Annex V of Directive 67/548/EEC. The IUCLID database, already adopted in 1999 by the International Council of Chemicals Associations (ICCA), has become the reference database for the world chemical industry for the collection and distribution of chemical data, and has now been enlarged to contains the revised section on Biocides. The second IUCLID CD-ROM was released in August 2000. In its present form, it contains data on 2604 high production volume chemicals, including all available data on the toxicological and eco-toxicological effects of these substances, together with summaries of risk assessment reports, where available, and other background information.

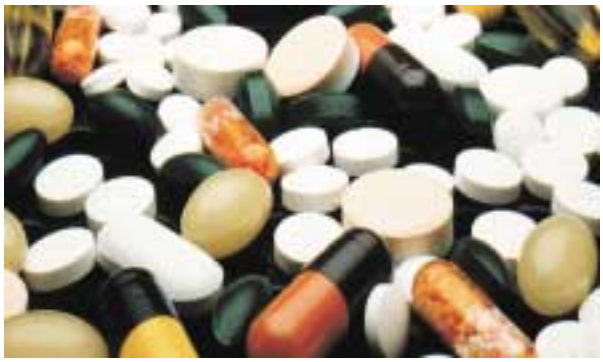
## European Centre for the Validation of Alternative Methods (ECVAM)

The European Centre for the Validation of Alternative Methods (ECVAM) is the international reference centre for the development, and scientific and regulatory acceptance of alternative testing methods, e.g. in vitro studies using cell tissue cultures, computer based testing and the use of non-invasive technologies in human volunteers. This work aims at replacing, reducing or refining the use of laboratory animals and is applicable in many different fields of the biomedical sciences.

Three scientifically validated in vitro methods (two for skin corrosivity and one for phototoxic potential) were accepted by EU Member States as Annex V test guidelines in relation to Directive 67/548/EEC. The ECVAM Scientific Advisory Committee endorsed the local lymph node assay for skin sensitisation and the EpiDerm skin corrosivity test as validated methods, and an ECVAM formal validation showed that three in vitro tests for embryotoxicity had met the validation criteria for the study.

In vitro assays for haematoxicity are successfully being applied to pesticides, with both human and animal cells. Standard operating procedures for the use of human spinal cord blood cells in clonogenic assays have been produced. An important contribution to the derivation of structure-activity relationships for predicting the corneal permeability of chemicals and pharmaceuticals has been published.





## Support to Pharmaceutical Regulation (SPR)

The SPR Unit provides management information/communication systems for the pharmaceuticals regulatory process. These tasks largely consist in the safety validation of medicinal products such as pharmaceuticals, vaccines, blood derivatives, radiopharmaceuticals and homeopathic medicines, as well as biotechnological derivatives, to ensure that citizens' health is protected.

Support to EMEA is being strengthened, in order to develop the Unified Tracking System (UTS) by integrating currently distinct marketing authorization procedures with up to date telematic solutions: EudraTrack Mutual recognition (EMR) and Application Tracking System (ATS). UTS is a telematic system for tracking all marketing submissions of medicinal products in Europe and it is capable of detecting improper submissions.

Additional activities in this area include the design and implementation of a centralized database service (named MINE), which gathers all scientific, efficacy and safety information on medicinal products which are authorized within the EU.

The EudraNet network (EudraNET II) is being upgraded, by adding the modules VPN (Virtual Private Network), including PKI (Public Key Infrastructure), and aims to increase the use of the currently used EudraNet I dedicated network services.

## Biomedical Materials And Systems (BMS)

The work programme REMED (Reliability of medical devices) focuses on (a) the development, improvement and characterization of biocompatible and bioactive surfaces (in terms of tissue compatibility and duration), in particular to improve haemocompatibility of cardiovascular grafts, stents, cathethers, and the osteointegration of hip and knee replacement prostheses; (b) on release from implant materials (orthopaedic and dental implants); and (c) on performance testing of biomedical devices, in support of harmonization of test methodologies on release from and performance of medical devices, under clinically relevant conditions, using a combination of advanced techniques, and in support of Directive 93/42/EEC.

A 2-axis dynamic loading station for a hip joint simulator was designed and constructed. Tests have started on programmes which can be performed with up to three million simulated walking cycles.

Pre-normative research in support of the Nickel Directive 94/27 was carried out, with the definition and publication of selected test methods (EN 12472) being adopted by the European Committee for the Standardization (CEN).

The work programme MIMES (Minimally Invasive Medical Systems) deals with medical imaging and therapy. While the diagnostic part related to PET was reduced in 2000, the section involved in the development of optical imaging techniques for minimally invasive diagnostics and therapy was enlarged.

A Fluorodeoxyglucose (FDG) production facility has been installed on the Cyclotron premises. The module, complete with target, synthesis module and quality control unit can deliver about 40 GBq at the end of each run. Clean rooms (class C and B) are also available for handling the tracers and to comply with GMP guidelines related to radiopharmaceutical production. Discussions have already started with some companies concerning the production of radiotracers (renting of the facilities) to release JRC staff from routine production.

The European Network for Optical Methods of Medical Diagnosis and Monitoring of Diseases (MEDPHOT) was launched within the framework of a thematic network exercise, with the BMS Unit acting as network manager.

# Management Highlights

This chapter presents a review of achievements in horizontal/coordination activities,which range from defining strategic directions and workprogrammes, to project and total quality management, communication and marketing, training, information technology and support activities (safety, infrastructure, financial and personnel administration).

## Total Quality Management

The IHCP committed itself to TQM in November 1999. A Total Quality Manager was appointed and took up his duties on March 16, 2000. A "self-assessment" exercise took place in 2000. 3 improvement teams were formed to handle the areas described below.

### Communication

To improve dissemination of information within the Institute, an Institute intranet web site has been created *(http://ihcp-agora'.jrc.it)* and is operational since July 2000. It was conceived as a repository of information on internal procedures, guidelines, information concerning the daily life of the Institute and utilisation of resources, e.g. staff situation, arrivals/departures etc. It incorporates the Units' periodically issued newsletters and it also contains the possibility to exchange ideas and a space - the Director's corner - where staff have a direct line with the Institute's Director.

### Project Management and Processes

A system to facilitate project reporting is being developed. It will consist of a repository for project information and common reporting formats. Various administrative processes were reviewed and new schemes implemented. Attention is being focused on planning processes and internal document flow.


- Customer survey

As an integral part of TQM, a customer survey was held among the IHCP's main institutional customers. The results showed that the IHCP is highly rated for its scientific/technical work, expertise, quality of its results and capability for fast response to emergency situations or extraordinary requests.

- Team Building Day

In response to the findings of the "self-assessment exercise", which requested improved corporate identity; a special team-building day was organized on 27 September 2000. The event was attended by almost all staff and was very successful.

- Job descriptions

In the frame of the general European Commission administrative reform, a complete revision of job descriptions (tasks, duties etc.) took place in July 2000.

## Prizes and Awards

The work performed on mycotoxins resulted in the award of a prize. Two proposals were selected in the JRC innovation competition project: the first one on the refinement and commercialisation of a genetically engineered neuronal model for toxicity testing and the second one on a novel plasma reactor to treat the inner surface of narrow tubes (e.g. catheters). A prize was awarded for the best paper published in ATLA (Alternatives to Laboratory Animals) to the group working on reprotoxicity and cardiotoxicity, who participated in the successful validation of the embryonic stem cell test.

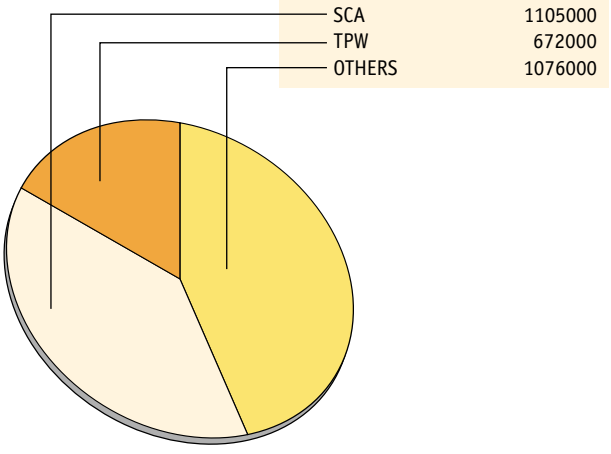
## Financial Indicators

Significant changes have characterized budget evolution in the year 2000 with the revision of the workprogrammes, which reflect on the organizational structure and resource utilization.

Extra funds have been received for the GMO area; the LEPEC activity on electronic commerce has been ceased and transferred to the Institute for Systems, Informatics and Safety (ISIS), allocating the related human resources to work on pharmaceutical regulation support. In the biomedical area, two workprogrammes have been discontinued (COCO: on release of consumer products where there is neither demand, nor a clear customer; and FUNSYS: on functional systems, which has been integrated into REMED) and funds have been re-allocated in the two remaining areas, to strengthen the emphasis on the demands of an ageing population and the need for better medical tools.

Competitive activities were undertaken in addition to the institutional budget. This has allowed, the enlargement of the IHCP network base. Far to be a pure economic incentive, these actions can be considered as a real indicator of the quality of the work performed and enable the Institute to increase its expertise and competencies.

Competitive actions (€)




Institute IHCP 2000 - Execution by programme line (K €)
(including competitive activities)

| PROJECT | Staff cost | Credits | TOTAL |
|---|---|---|---|
| Control of Quality & Safety of Food & Related Items | 4391 | 1725 | 6116 |
| Support to the implementation of Community Policy on biotechnology (GMO) | 1116 | 750 | 1866 |
| | **5507** | **2475** | **7982** |
| Validation of alternatives methods (ECVAM) | 3849 | 2347 | 6196 |
| Chemical Products, environmental risk assessment (ECB) | 5145 | 1054 | 6199 |
| Telematic system for the EU pharmaceutical regulatory activity (ETOMEP) | 2377 | 590 | 2967 |
| LEPEC, Consumer Protection Lab. Valid. Monitor. For Electronic Payment | 861 | 160 | 1021* |
| | **1232** | **4151** | **16383** |
| Reliability of Biomedical Devices (REMED) | 4055 | 329 | 4384 |
| Contam. of Nutrition & Consumer Prod due to Material Rel. ("COCO") | 2097 | 425 | 2522* |
| MITRA, Medical Imaging and Therapy using Radio-tracers | 804 | 90 | 894 |
| Functional systems for Health and Consumer Protection | 1371 | 48 | 1419* |
| | **8327** | **892** | **9219** |
| **TOTALS** | **26066** | **7518** | **33584** |

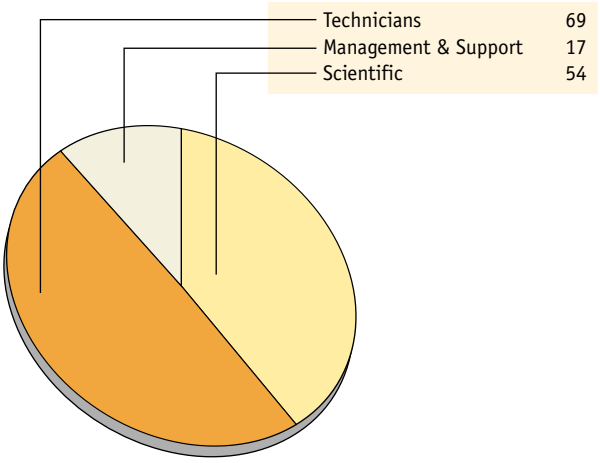
* Work programme revised or stopped during 2000

**FOOD**
**CHEMICALS**
**BIOMATERIALS**

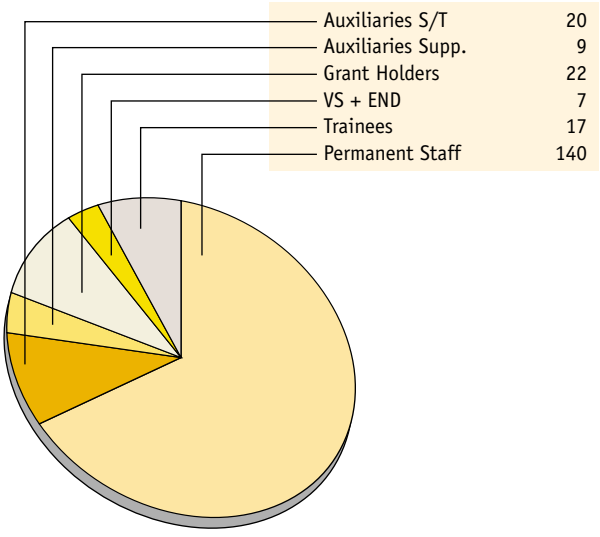
## Personnel

Due to the revision of the workprogrammes and the boost in some areas such as GMO, there has been an increase in the nominal staff table, up to a total of 167 staff members. The IHCP can count on 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. The actual average staff number was 140 in 2000, with positions vacant due to retirements and departure of short-term personnel. Suitable replacements need to be found in key specialized areas such as toxicology, molecular biology etc. A large contribution to Institute activities is made by temporary staff (auxiliaries, national experts, visiting scientists etc.) as well as PhD and Post Doc grant holders, for whom an extensive recruitment campaign has been carried out.

Permanent staff average year 2000




Total staff average year 2000




## Training

Training activities are being concentrated on the transfer of key competencies to scientists from "candidate" countries for EU membership and developing countries, with emphasis on training of young researchers. Several examples can be given: training offered to the World Health Organization (WHO), sessions organized for the use of the IUCLID database on chemicals and additional training courses related to detection methods for GMO/food safety issues. It is also worth mentioning some single training actions whereby Stagiaires and Ph.D. students are hosted either to complete their studies or to develop expertise in a subject. The intention is to intensify these activities: publicity has been made in specialized magazines and on specific web sites (e.g. Marie Curie fellowships). In-house staff training has also been emphasized: examples include safety and specific technical subjects.

## Informatics

In the context of the Communications Improvement Team work, a pilot project was initiated which will serve as a showcase of modern IT-based communication technologies. The features of Windows 2000 and Exchange 2000 (with standard Commission products) will provide a standard working environment for all IHCP users.

## Safety

Safety is a matter of great concern at IHCP, given the requirements of Italian Law nr. 626/94, the peculiarity of certain installations (e.g. Cyclotron), laboratories of the Institute, and QA/QC prescriptions. Over and above such requirements, it is considered an integral part of Institute management to guarantee staff healthy working places in which work can be carried out safely and in the best conditions.

The work on safety, prevention and protection has been embodied in the "Safety project 2000" plan, elaborated on the basis of the safety analysis carried out in 1999 to fully comply with law 626/94.

Emergency and evacuation plans have been issued. Fire risk evaluation has taken place and been reported (including all electric and electronic appliances) and an intervention plan has been issued. Periodical checks and inspections are performed, without prior notice, following a hazard checklist. The ergonomics of working places have also been studied.

An intensive training campaign on safety is taking place. In particular, 45 safety information courses for newcomers were given in 2000 as well as two specific courses for the persons responsible for safety in buildings. Courses for specific teams working in the same environment have been formulated and just started (3 courses in 2000).

## Infrastructure

Beside the concentration of staff in a limited number of buildings, major work has been carried out to re-structure a building to host food loboratories and to re-structure another one to host additional GMO laboratories.

## External Communication

### Press and media coverage

This year the IHCP received extensive press coverage: articles were published in well known newspapers such as The Wall Street Journal, il Corriere della Sera, il Sole 24 Ore, etc. Coverage was given in local newspapers and a special report on food safety and GMOs was published in the magazine Famiglia Cristiana. The BBC, RAI, and Euronews journalists visited the IHCP laboratories. A tele-training experiment was also carried out, for the Regione Lombardia authorities, presenting activities related to coatings of biomedical implants (prosthetic devices).

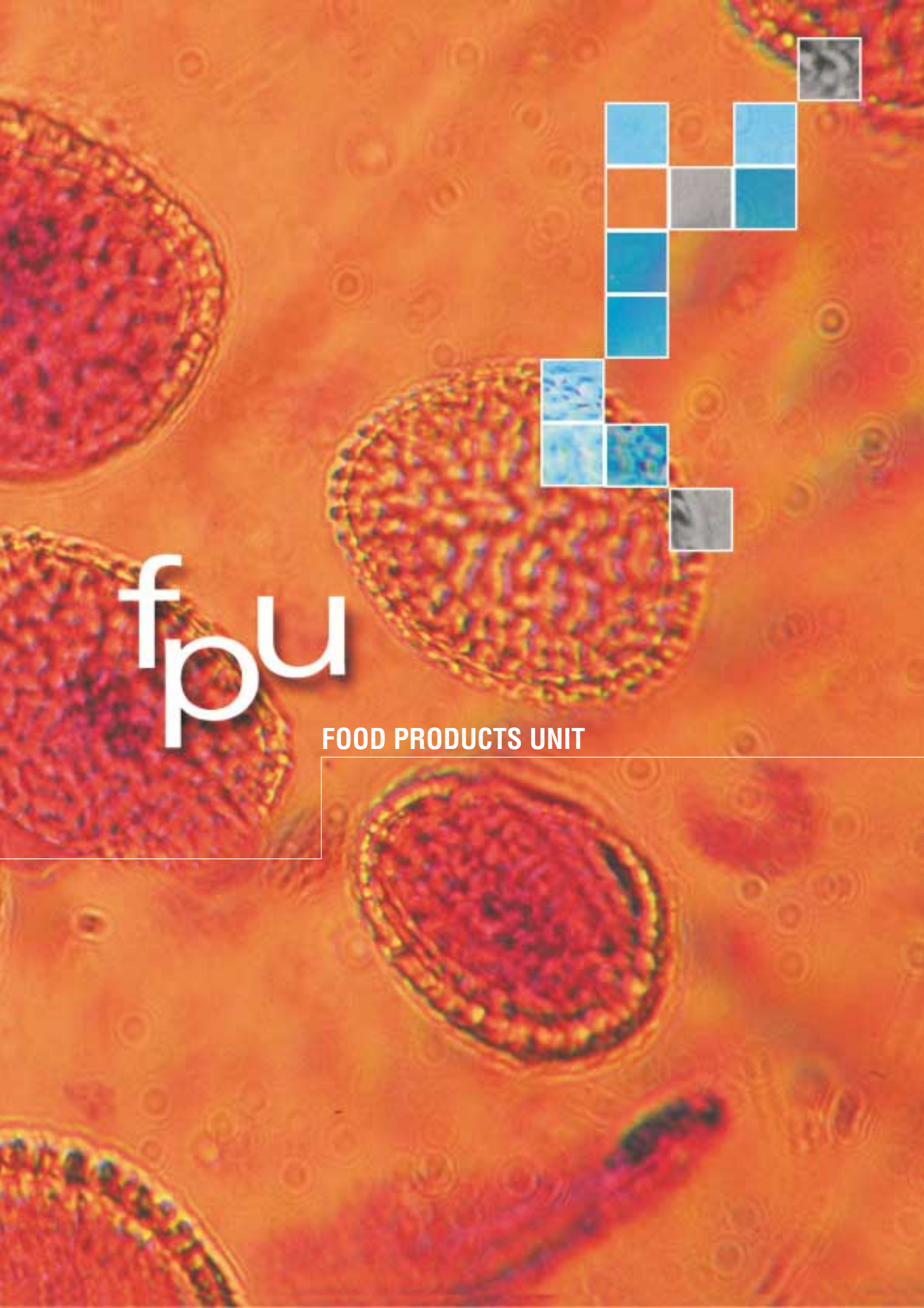
### Documentation

A brochure was published in 2000 to illustrate IHCP's research activities. The brochure was distributed to the press, the general public, to our partners and to political decision makers. Various information leaflets, flyers, project sheets, and posters were printed and distributed worldwide.

The Institute web site *(http://ihcp.jrc.it)* was created and came into operation in January 2000. It provides a description of the institute, its mission and objectives, an overview of activities, contact persons, a description of work opportunities (for grantholders, visiting scientists etc.) and opportunities for collaboration and partnership. It also contains links to specific project sites, containing detailed descriptions. The Institute web site can also be accessed through the JRC web site *(http://www.jrc.cec.eu.int)*.

### Events

General events worth reporting include contributions to the exhibition at the European Parliament in February, participation in "Eurosalute" in Milan in October, organization of various meetings on genetically modified organisms and the chemicals policy. The JRC's Open Day in May saw a total of more than 1500 visitors to IHCP facilities/laboratories. The visits of Commissioners Philippe Busquin and David Byrne and the visit of EU President Romano Prodi were very important for the IHCP. The Italian President Carlo Azeglio Ciampi and the Italian Research Minister, O. Zecchino, also visited the IHCP. Visits to laboratories were organized for the President of CNR, Lucio Bianco, the Finnish parliament's Committee for the Future, EP INDU members, the Industrial Union, and the JRC Alumni event. The IHCP had over 200 official visitors during the year.


fpu
FOOD PRODUCTS UNIT

**Web Information resources**

**At IHCP site:**
*http://ihcp.jrc.it/TheIHCP/Activities/ACTSafe.html*
*http://ihcp.jrc.it/TheIHCP/Activities/ACTRele.html*
*http://ihcp.jrc.it/TheIHCP/Activities/ACTGMOs.html*

**At the Food Products Unit Site:**
Food safety: *http://food.jrc.it/activities/safety/index.htm*
Food quality: *http://food.jrc.it/activities/quality/index.htm*
European Wine Databases: *http://food.jrc.it/activities/bevabs/index.htm*
Contact Materials: *http://food.jrc.it/activities/contact/index.htm*
Genetically Modified Organisms: *http://food.jrc.it/activities/gmo/index.htm*
GMOs in Food and Environment: *http://food.jrc.it/gmo/*

In order to meet customer research and support needs, the FPU addresses two major areas: (1) activities within the field of food safety and quality and (2) issues on genetically modified organisms. During 2000, the FPU focussed its many activities into three areas of food safety, namely a) support to research on transmissible spongiforme encephalopathy (TSE) b) residues and contaminants, and c) contact materials. Likewise, the projects on food quality have been concentrated into a) authenticity of wine and b) vegetable fats and chocolate.

## Food and Feed Safety

### Support to research on Transmissible Spongiform Encephalopathies (TSE)

Animal meal containing high-risk material is conceived as the primary source of BSE. In order to inhibit a further spread of this disease, the European Commission imposed a ban on the use of animal meal from mammals in feed for ruminants (Commission Decision 94/381/EC). The FPU provides scientific expertise for the establishment and enforcement of suitable regulations. Currently, there is only the microscopic technique (an official European method) for tests to support enforcing the ban, though this approach has some major drawbacks. There is a need for other methods that are more suitable for routine analysis and allow a high throughput of samples.

The FPU started searching for more appropriate methods that could be validated. A promising technique (developed in the U.K.) based on enzyme linked immunosorbent assay (ELISA), was validated by the FPU. The method proved to be suitable for this specific purpose and other European laboratories can successfully perform this method.

Future FPU activities in this field will focus on the use of other screening methods such as fourier transform near infrared spectroscopy, differential scanning calorimetry and pyrolysis mass spectrometry, for proof of animal proteins in feed. In 2001 FPU will also be cooperating in an EU funded shared-cost action project, aimed at developing and validating methods for the detection of mammalian tissues in feed. FPU will also contribute to setting up a sample bank and library of microscopic images on the Internet.

Safe rendering of animal by-products is an important measure for preventing the spread of BSE. Since 1996 rendering of animal waste must be performed at 133°C, 3 bar for 20 minutes. Although rendering plants are required to record temperature and pressure, it is hard to understand whether animal meal of unknown origin has already been treated according to this legislation. In 1998 the FPU validated a method based on ELISA to prove whether appropriate sterilisation of animal meal has taken place. This method works well but has the drawback of requiring the animal waste to contain at least 10 % pork. To circumvent this problem the FPU recently optimized an existing ELISA method for beef and evaluated this test kit by performing an in-house validation study. Considering the positive results of this study, the FPU is currently validating the method by carrying out a collaborative trial.

### Central nervous tissue (e.g. brain) in meat products

The emergence of a new variant of Creutzfeldt-Jakob disease during the BSE epidemic led to the ban on the use of specified risk materials (SRM) as a measure to minimize human exposure risk to BSE. The tissues of the central nervous system account for 95% of the infective load in a BSE-case approaching the end of the incubation period. Central nervous tissues (CNT) such as brain and spinal cord are among the SRM whose removal at the slaughtering stage must be ensured by permanent official control. The SRM must be incinerated to avoid their inclusion in the food chain.

The FPU has initiated a new activity in collaboration with the University of Leipzig, dealing with the determination of CNT in final meat products. This new field of research responds to the need to assess human exposure risk to transmissible spongiform encephalopathies (TSE) via the food chain. The detection of CNT in the final thoroughly homogenized and heat treated meat product has recently been achieved by Professor Luecker of the University of Leipzig.

The FPU is now organizing a collaborative study with the participation of official control laboratories. The final validated method will help to establish an important measure of control throughout Europe, in addition to the existing or forthcoming prohibition of SRM and will also help to control imports of final meat products from third countries.

## Residues and Contaminants

### PCBs in food and feedingstuff

The reason for the high concentration of PCBs (polychlorinated biphenyls) discovered in pork and poultry during the Belgian crisis, was found to be contaminated feedingstuff. In order to enforce the ban on feedingstuff containing PCBs, (Commission decision 1999/788 /EC), it was therefore of the utmost importance to analyse a high number of feed and food samples. The FPU developed and validated two analytical methods which allow a great increase in the throughput of samples. The FPU is currently organizing a ring trial on detection of PCBs in feed with 27 laboratories from 14 Member States. A serious bottleneck in PCB analysis, in terms of test duration, is the extraction step. The FPU has started to employ more rapid techniques such as "pressurized solvent extraction" to analyse feed samples, following conventional analytical methods (GC/MS). Considering the encouraging results of this study, the FPU will combine this extraction method with immunoassay technology in our future research activities, in order to achieve a further improvement of PCB analysis.

### Mycotoxins

Research on mycotoxins in the FPU focussed on several important fields in support to European legislation and issues of emerging interest for consumer protection. A pre-requisite for the monitoring of contamination lies in precise analytical methods. These highly toxic metabolites (aflatoxins) which can be found in food and feed are regulated by Directive 1998/1525/EC, while contamination problems in imported food have already led to European wide import bans (EU Decisions 1997 /613/EC and 1999/356/EC).

The FPU has already developed and validated state-of-the-art analytical methods based on liquid chromatography combined with an immunoaffinity clean-up step. In 2000 special effort was put into the development of very simple and precise methods, which can be used as monitoring tools by developing countries to check compliance with EU legislation for export purposes. The main reason for this activity is that developing countries are producers of food which is susceptible to aflatoxin contamination (e.g. peanuts, pistachios, figs, corn and spice).

The FPU has produced a method based on the easy-to-use principle of thin-layer chromatography (TLC) which is suitable for monitoring aflatoxins at European legislative limits. In addition, two novel and simplified devices for the quantification of aflatoxins were developed. A patent has been filed for one of these novel densitometers and a staff member of the FPU received the "Bruno-Rossmann-Preis 2000" from the German Chemical Society (Gesellschaft Deutscher Chemiker) for this innovative approach. Another device based on a modified office scanner was produced in collaboration with the Fraunhofer-Institute for Optics in Jena (Germany).

Underlying research has also been performed in the area of improvement of derivatization techniques for the determination of aflatoxins in various food matrices. A direct comparison between two derivatization systems involving the bromination and UV irradiation techniques was performed, showing the suitability of both techniques. In addition, a multi-method for screening and quantification of several mycotoxins in one analysis run has been developed.

## Contact Materials

Natural and synthetic materials such as plastics, paper and board, metals and ceramics are commonly used to manufacture consumer goods and for food packaging. The safety of such materials relies on ensuring that there is no migration of substances at unsafe levels from the material to food or to humans during contact. The activity on contact materials targets consumer goods such as children toys and food packaging materials.

### Food packaging

Safe and high quality food supplies rely on being efficiently protected from deterioration. Various food contact materials and ingredients can be used for food packaging as long as they do not pose health concerns to consumers, which may occur when some substances migrate from the food packaging into the food. Migration is the only parameter that originates from the packaging itself and may cause it to inadvertently affect the food or pose health concerns to the consumer.

Migration of substances used in organic coatings and lacquers for food cans may raise concern for human health. For example, in recent years Bisphenol A diglycidyl ether has been reported by several Member States in concentrations higher than the permissible level stated in Directive 90/128/EEC. Recently, the FPU has performed extensive surveys on various canned market products.

Canned foods typically have an extremely long shelf life (up to 3 years) and high heat sterilisation treatment; therefore it is necessary to understand the effects of temperature and storage on migration of BADGE. A project on kinetics of migration and degradation of BADGE was completed after 1-year storage.

For a better understanding of the migration potential of various coating substances, a joint industry project was carried out on the effects of the composition of can coatings on migration of BADGE, BFDGE, their degradation products and substitutes. Migration levels were low in all cases.

Contaminants in polycarbonate baby bottles can contain a residual proportion of Bisphenol A (BPA) due to manufacturing and/or subsequent processing. Bisphenol A has been considered to be an endocrine disruptor and it is important to monitor the absence of migration of such substances from articles and contact in food. A worst-case methodology for migration measuring was applied to a European survey of baby bottle samples from all EU Member States. The results showed that migration remained below the specific migration limit laid out in Directive 90/128/EEC.

Refined soybean oil has been extensively used in the plastics industry in the form of epoxidised soybean oil (ESBO). ESBO is primarily used as a plasticiser and stabiliser for polyvinyl chloride (PVC) and other plastic materials. One common application of ESBO is in the PVC lining of baby food glass jars. The FPU initiated a project on the determination of ESBO used in the sealing ring for vacuum-packed baby food jars. An improved methodology was implemented for the analysis and a monitoring study is under progress on more than 250 jars collected in all EU Member States.

A European Database of substances used in materials and articles in contact with food has been made available to the public. These substances are being gathered in a reference collection, characterized physico-chemically and are available at the FPU. To facilitate access to European Commission documents and provide a public service with relevant information, the FPU developed an Internet site dedicated to food contact materials (http://cpf.jrc.it/webpack). It contains legislative information in downloadable format as well as information on contacts with authorities and organizations in the field of food contact materials, and methods for overall migration. A satellite site (http://cpf.jrc.it/smt) is dedicated to physicochemical and spectral information as well as analytical methods on an increasing number of regulated substances.

### Toys and childcare articles

It is particularly important to assure the safety of the youngest consumers: babies and infants. Since common consumer goods may be in prolonged contact with babies' mouths, a potential migration of substances through membrane contact would have a stronger effect on their smaller bodies. Phthalates are typically used as softeners in soft PVC toys and childcare articles. Renewed health concerns regarding these substances recently resulted in a temporary ban on the use of phthalates in toys (Commission Decision 1999/815/EEC). This has given rise to the need not only for estimating the potential exposure of infants to a variety of phthalates by mouthing such toys, but also developing the means to test these toys or childcare articles with mechanical means. The FPU is currently co-ordinating the validation of 2 methods at a global level. The FPU will extend the investigation to the migration of other plasticisers.

### Vegetable fats in chocolate

The new European Chocolate Directive 2000/36/EEC now allows the addition of up to 5 % of vegetable fats, the so-called cocoa butter equivalents (CBEs), other than cocoa butter (CB) in chocolate products. The following permitted fats are specified in the directive: palm oil, illipé (Borneo tallow or tengkawang), sal, shea, kokum gurgi and mango kernel. In addition to the mandatory labelling of the addition of vegetable fats other than cocoa butter, labelling to indicate that those fats have not been added is also allowed. Appropriate testing methods are the pre-requisite for implementation of the Directive. In order to facilitate the analysis, the FPU (in collaboration with the Institute for Reference Materials and Measurements) is certifying a cocoa butter reference standard. A pre-certification study was carried out in 2000 and the materials have been prepared. The certification exercise will be completed in 2001. However, there is still a perceived need within official control laboratories for rapid screening methods for the quantification of such vegetable fats in chocolate in order to implement the new directive and to handle a large throughput of samples. The FPU has therefore recently developed a simple and reliable analytical approach, which will be validated in an international ring test in 2001. In addition, the FPU has investigated appropriate methods to gain information about the analytical threshold (in case of negative labelling).

### Polyphenols - making chocolate a functional food?

Today it is widely accepted that a healthy diet or the intake of certain dietary components can contribute to achieving optimal health and development. Reducing the risk or delaying the development of cardiovascular disease, cancer and other age-related diseases are also important factors. Recently, polyphenols have gained attention as non-nutrient compounds of our diet (e.g., in fruits, fruit juices, tea, red wine and chocolate), owing to their antioxidant capacity and their possible beneficial implications to human health. However, there is still a need for suitable methodologies to quantify polyphenols in food and to show their bioavailability from diet. Therefore, to obtain reliable data on polyphenol content in foods, a complete methodology based on modern analytical techniques has been set up for the analysis of chocolate polyphenols.

### Authenticity of Wine

Since wine has always been subject to fraud, the European Union has created strict regulations to protect the European consumer from adulterated products. The European office for wine, alcohol and spirit drinks (BEVABS) was established as part of the IHCP in 1993. Its aim is

to manage a database on authentic European wines (started in 1991) to combat major fraud in the wine sector. BEVABS provides the basis to share experience at European level with the aim of improving and harmonizing the control of wine products and strengthening the European network of control laboratories using isotopic techniques. It co-ordinates the EU Wine Databank activities as well as the need for training and transfer of know-how to new Member States Laboratories.

### Wine Databank

Apart from the collection of isotopic data from the 1999 vintage, a number of actions have been undertaken to improve the control of wine. The development of the new software “Db Wine” for the management of the EU wine data bank has been completed.

### Improved analytical methods

Another important step forward in 2000 was the proposal of a method for measuring of the carbon-13 isotopic content in wine ethanol. This is now on its way to being adopted as an official method. Finalizing the official adoption of a number of methods for the analysis of spirit drinks for an EU regulation is the direct outcome of a shared cost action project (SPIRITS) in which BEVABS was one of the main partners. The first 4 methods (alcohol grade, dry extract, density and congeners) were included in the EU regulation EC 2870/2000 on spirit drinks. Wines suspected of adulteration were taken from the European market for analysis at the request of the “Office de Lutte Anti Fraudes” (OLAF) anti-fraud inspectors.

## Genetically Modified Organisms (GMOs)

There has been intense public and political debate on GMOs and how they relate to environmental, food and feed safety. The moratorium for EU approval, introduced in June 1999, is still in place. In addition, Member States have called for Commission Decisions. The GMO debate is also ongoing in non-EU countries.

### GMOs in the environment

For a number of years the IHCP has been collecting cases from Member States, describing the summaries of deliberate field trials involving GMOs that are carried out for research and development purposes. Software had been developed that allows Member States to exchange data with the JRC and a WWW site had been created (http://biotech.jrc.it/) where an up-to-date overview can be consulted.

### GMOs in food

Assessing the compliance of food products with the European Union GMO Regulations is based on detection, identification and quantification. The analytical methods for detection must be sensitive and reliable enough to obtain correct results in all control laboratories. Since detection becomes more difficult after processing, in 2000 the FPU validated another screening method for the detection of GMOs in highly processed food samples such as biscuits. Specific information has to be available for the identification of GMOs. In addition, detection cannot take place without knowledge of the details of the molecular make-up of the GMOs. The FPU is in the process of setting up a molecular register, which, besides the scientific data, also contains the tools for control authorities to design appropriate identification methods. In 2000 the FPU validated a method to quantify the amount of GMOs in raw materials. The results of the validation study have shown that in this specific case about 70% of correct results are obtained for 1% GMO-containing raw material. Sound methods can only be developed if appropriate reference samples are available for GMOs. The Institute for Reference Materials and Measurements (IRMM) takes the lead in the production of these samples. The FPU has collaborated intensively

with IRMM on the development of appropriate production protocols and on the characterization of the reference samples produced.

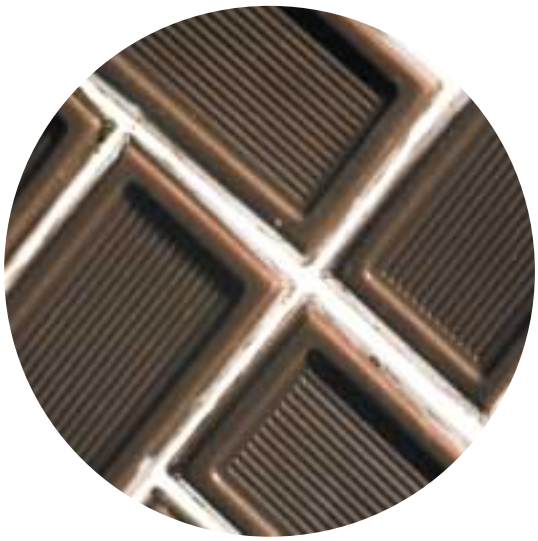
### "European Network of GMO Laboratories"

A "European Network of GMO Laboratories" was created in 2000 and is being organized and coordinated by the JRC. 38 experts from national enforcement laboratories and 18 European Commission representatives from various services held a first meeting in June to discuss technical issues for the implementation of EU biotechnology regulations. The scope of this meeting was to understand the needs of the Member States' reference laboratories on GMO detection in order to have a technical dialogue and to prioritize the most urgent questions to be addressed. Discussions focussed purely on scientific matters and identified the need for the creation of the following specific working groups to cover:

- Appropriate protocols for validation studies and for proficiency testing.
- Appropriate reference materials.
- The design, content and function of a molecular register.
- Compatibility between methods and the eventual requirements for further research to understand the appropriateness of DNA and protein based methodologies.

## Training

The FPU and the World Health Organization (WHO) co-organized a series of laboratory training courses on "The Analysis of Food Samples for the Presence of Genetically Modified Organisms". Four training courses (each lasting one-week) were carried out in the FPU's GMO Laboratory in 2000. Participants came from member states, accession countries and from many other countries throughout the world. Training will continue in 2001.



### Shared Cost Actions and other competitive projects

During 2000, the FPU was partner in 10 shared cost action (SCA) projects.

In the course of 2000, 6 proposals for share cost actions were submitted.

### Support to CEN (European Committee for Standardization)

In 2000 the Food Products Unit 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.

### Publications 2000


Gilbert J., Simoneau C., Cote D. and Boenke A., *"An internet compendium of analytical methods and spectroscopic information for monomers and additives used in food packaging plastics"*, Food Add. Contam, 17, 889 (2000).

Lipp M., Anklam E. and Stave J.: *"Validation of an immunoassay for the detection and quantification of Roundup-Ready soy beans in food and food fractions"*, J. AOAC Internat. 83, 919 (2000).

Simoneau C., Lipp M., Ulberth F. and Anklam E.: *"Quantifica-tion of cocoa butter equivalents in mixtures with cocoa butter by chromatographic methods and multivariate data evaluation"*, Eur. Food Res. Technol., 211, 147 (2000).

Stroka J., Anklam E., Jörissen U. and Gilbert J.: *"Immuno-affinity column clean-up with liquid chromatography using post-column bromination for the determination of aflatoxins in peanut butter, pistachio paste, fig paste and paprika powder: a collaborative study"*, J. AOAC Internat., 83, 320 (2000).

Stroka J., Petz M. and Anklam E.: *"Analytical methods for the determination of aflatoxins in various food matrices at concentrations regarding the limits set in European Regulations: Development, characteristics and limits"*, Mycotoxin Res. 16, 23 (2000).

Theobald A., Simoneau C., Hannaert P., Roncari A., Rudolph T. and Anklam E.: *"Occurrence of bisphenol-F-diglycidyl-Ether (BFDGE) in fish canned in oil"*, Food Add. Contam, 17, 881 (2000).

Von Holst C., Honikel K.O., Unglaub W., Kramer G. and Anklam E. *"Determination of an appropriate heat treatment of animal waste by using the ELISA technique"*, Meat Sci. 54, 1 (2000).

Wollgast J. and Anklam E.: *"Polyphenols in chocolate: is there a contribution to human health?"*, Food Res. Internat 33, 449 (2000).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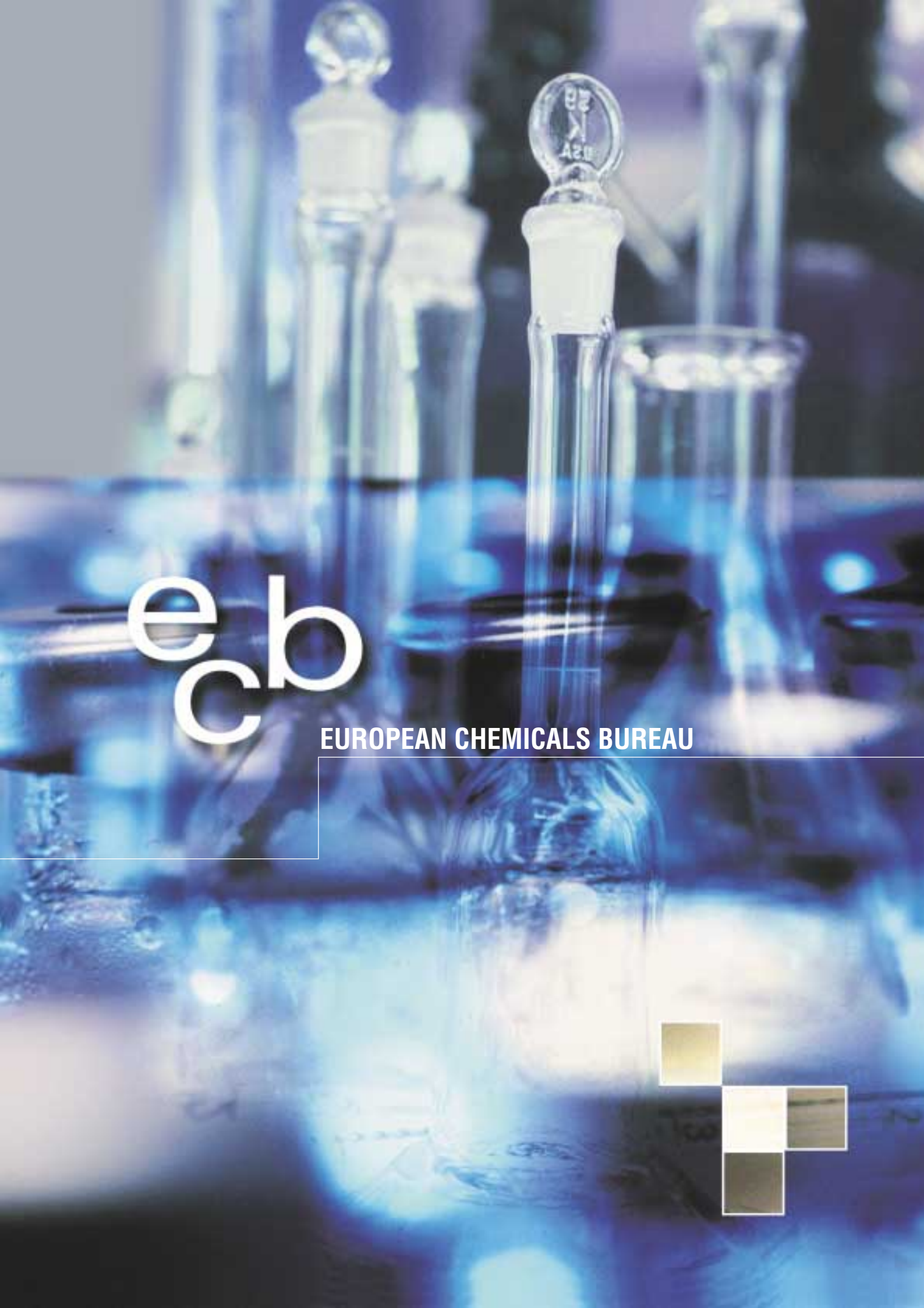

ecb
EUROPEAN CHEMICALS BUREAU

European Chemicals Bureau

**Web Information resources**

**At IHCP site:**
http://ihcp.jrc.it/TheIHCP/Activities/ACTChem.html

**At the European Chemicals Bureau site:**
Home Page: *http://ecb.ei.jrc.it/*
Existing Chemicals: *http://ecb.ei.jrc.it/existing-chemicals/*
New Substances: *http://ecb.ei.jrc.it/new-chemicals/*
Biocides: *http://ecb.ei.jrc.it/biocides/*
Classification and Labeling: *http://ecb.ei.jrc.it/classification-labelling/*
Testing methods: *http://ecb.ei.jrc.it/testing-methods/*
Import/Export: *http://ecb.ei.jrc.it/import-export/*

## Chemical substances: Risk Assessment

The European Chemicals Bureau (ECB), provides scientific and technical support to the conception, development, implementation and monitoring of EU policies on dangerous chemicals. It represents the focal point for collecting information on new and existing chemicals and manages the assessment of risks (hazard and risk assessment) posed to workers, consumers and the environment. It supports legal classification and labelling, the notification of new substances, information exchange on import and export of dangerous substances, the development and harmonisation of testing methods and the authorization of biocides. 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.

A new chemicals policy is being established in the EU. IHCP, through ECB and ECVAM, takes a central role in the establishment of this policy: further expansion of activities in this field is expected.

## Existing chemicals

ECB is responsible for the scientific and technical support to Council Regulation EEC 793/93, with regard to the first three steps of the Regulation, i.e. data collection, priority setting and risk assessment.

### Data collection

All data have to be submitted in the Harmonised Electronic Dataset (HEDSET) format and are managed by the International Uniform Chemical Database (IUCLID), both developed and maintained by ECB. IUCLID has been adopted as the standard database by the International Council of Chemical Associations (ICCA) and is now de facto the reference database for the World Chemical Industry to collect and distribute data on chemicals.

### Priority setting

In consultation with 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 man or the environment. Three priority lists have been published so far.

### Risk assessment

Substances on the priority lists must undergo an in depth risk assessment (following the Regulation EC 1488/94, implemented in the detailed Technical Guidance Documents (TGD) on Risk assessment for New and Existing Substances), covering the risks posed to man and to the environment. After adoption of the risk assessment, three publications are produced (comprehensive risk assessment report in 3 formats: book, IUCLID and ECB homepages, summary in 2 formats: book and ECB homepages and conclusions in the Official Journal).

### Specifically in 2000:

Upgrade of the database IUCLID to include the Biocides section. Release of the second IUCLID CD-ROM in August 2000.

High production volume chemicals in IUCLID has raised to 2604, including all available data on toxicological and eco-toxicological effects of these substances, together with summaries of risks assessment reports, where available, and other background information.

### New substances

Activities regarding new substances are carried out to fulfil the technical and scientific obligations of the EC regarding the notification schemes and risk assessment for all new chemicals made available in the EU, as laid down in the Directives 67/548/EEC and 96/67/EEC. In 2000, 400 summary notification dossiers were distributed.

240.000 Euros were assigned to the JRC for the ECB-NET project within the I.D.A. programme (Interchange of data between Administrations, http://europa.eu.int/ISPO/ida/ida.html), which involves a large number of customer DGs (DG AGRI, ENTR, ENV, MARKT, FISH, SANCO, EMPL, TREND).

The ECB project aims to develop a network for electronic data transmission between the ECB and competent authorities in the Member States. The project has been allocated funds for a preparative and a feasibility study. The work has been contracted out and will initiate early in 2001.

The ECB provides technical and scientific support for the implementation of the Directives 67/548/EEC, 93/67/EEC and 98/8/EC, and regulations 793/93 and 2455/92 as well as several other legal provisions.

## Testing Methods

The seven following methods are to be added to part C of Annex V:

- C.14. Fish, Juvenile Growth Test
- C.15. Fish, Short-Term Toxicity Test on Embryo and Sac-Fry Stages
- C.16. Honeybees – Acute Oral Toxicity Test
- C.17. Honeybees – Acute Contact Toxicity Test
- C.18. Adsorption/desorption using a batch equilibrium method
- C.19. Estimation of the Adsorption Coefficient (KOC) on Soil and on Sewage Sludge using High Performance Liquid Chromatography (HPLC)
- C.20. Daphnia Magna Reproduction Test

Method B.1. Acute Toxicity (oral, the classical LD50 test) will be deleted from Annex V.

During 2000 activities centred on continuing the development of Testing Methods for MMMF. Activities consisted in the calibration of the test on Sub-chronic Inhalation Toxicity of Synthetic Mineral Fibres in Rats and continuing the discussions with partners for the further development of the tests:

- Biopersistence of fibres after short-term exposure by inhalation.
- Biopersistence of fibres after intratracheal instillation.

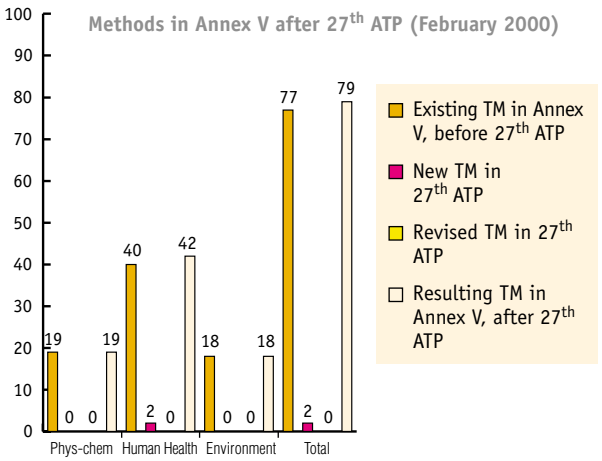
## New Chemicals

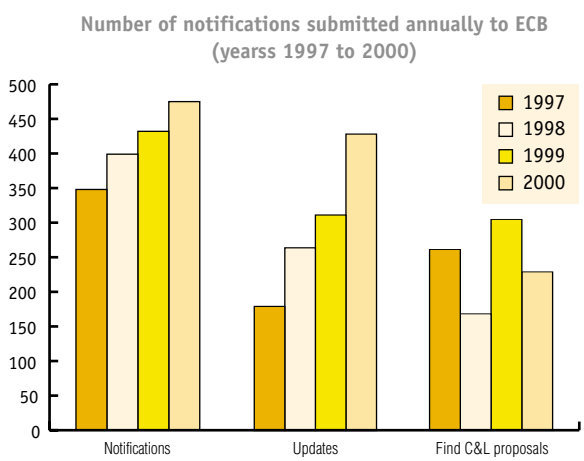
Totally, over 5000 notifications, including over 3000 substances, have been submitted since 1983, currently equivalent to about 400 notifications per annum. Irrespective of notification date, during the year 2000 a total of 900 dossiers (comprising 475 new notifications and 425 updates) were distributed from ECB to MSs. In addition, 227 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 1997, 1998, and 1999 (See table below).

Annual notification statistics since 1983, analysed by MS, show that over half have been combined contributions from the UK and Germany. With regard to the origin of the substances, about half the new commercial chemicals marketed in the EU during the year 2000 were foreign imports, principally from the USA.

### Terrestrial Model Ecosystems (TME) (project ENV4-CT97-0470)

The project analyses possible uses of Terrestrial Model Ecosystem (TME) data for regulatory purposes, focusing on current approaches for Environmental Risk Assessment for industrial chemicals, Biocides and plant protection products.




## Existing Chemicals

### Data distribution

The IUCLID CD-ROM "Year 2000 Edition", containing the phase II data and the updates for phase I submissions, was released in August 2000. The product is distributed through the Publication Office in Luxembourg.

### Risk assessment

During the first quarter of 2000, the 4th Priority List underwent both informal and formal Interservice Consultation and was finally adopted on 31 May 2000. This list contains priority substances for risk assessment reports, which are prepared by member States.

### Technical Guidance Documents

The ECB initiated the revision of the Technical Guidance Documents (TGD) in support of Commission Directive 93/67/EEC on risk assessment for new notified substances and the Commission Regulation (EC) 1488/94 on risk assessment for existing substances and on Directive 98/8/EC concerning the placing of the biocidal products on the market. This work will last several years.

## Classification and labelling

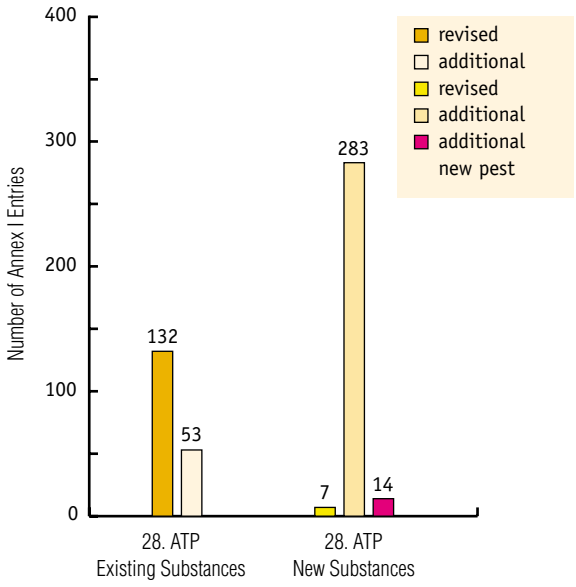
The 28th ATP was prepared and is waiting to be endorsed by the Member States at the TPC voting meeting in Brussels 25 January 2001. This ATP includes:

- Updated, corrected and recast version of Foreword to Annex I (incl. Tables 1A and 1B),
- Revisions of Annex I entries of 132 Existing and 7 New Notified Substances,
- New Annex I entries of 53 Existing, 283 New Notified and 14 New Active Pesticide Substances,
- Two deletions of Annex I entries (covered by other Annex I entries).

Risk assessment reports finalised in 2000

| | | |
|---|---|---|
| 3,4-dichloroaniline | 95-76-1 | DE |
| Diphenyl ether, octabromo der. | 32536-52-0 | FR*/UK |
| Bis(pentabromophenyl)ether | 1163-19-5 | FR*/UK |
| Methyl acetate | 79-20-9 | DE |
| hydrogen peroxide | 7722-84-1 | FIN |
| Toluene | 108-88-3 | DK |
| di-"isononyl" phthalate | 28553-12-0 | FR |
| 1,2-Benzenedicarboxylic acid, di-C8-10-branched alkyl esters, C9-rich | 68515-48-0 | FR |
| di-"isodecyl" phthalate | 26761-40-0 | FR |
| 1,2-Benzenedicarboxylic acid, di-C9-11-branched alkyl esters, C10-rich | 68515-49-1 | FR |
| tert-butyl methyl ether | 1634-04-4 | FIN |

*Human Health Only



## Export/Import

The ECB continues with the project in collaboration with UNITAR to develop a National Profile Homepage. This is an Internet site where all the information on national profiles has been produced by many countries either in collaboration with UNITAR or independently. The idea of such a profile is to create a national basis in order to understand the present state within the country and how to proceed towards better chemical management in the future. The site was made available to the public in 2000 at the address:
http://www.unitar.org/cwm/nationalprofiles/index.htm

The ECB finalized the Internet version of 20 national profiles during 2000, adding up to a total of 35 profiles on the web site. In addition, UNITAR and ECB are preparing a CD reflecting the web site for interested parties who have no web access.

A new web version of the EDEXIM database has been developed to assist the export notification system under the voluntary agreement. The database will then support the current Regulation contemporarily with the new yearly notification system.

## Biocides

As a follow-up to the Directive, the Council agreed on the review regulation for existing active biocidal substances proposed by the member states in September 2000. The ECB prepared the technical issues around the implementation of the review regulation.

The main issue solved was that on the waiving of data requirements and an updated version of the guidance document was placed on the web in October 2000. Updated versions of two other guidance documents on Annex I (approved active substances) entry and product evaluation were circulated to the member states for discussion in January 2001. The revision of the risk assessment guidance document for new and existing chemicals and biocides was brought forward.

Exposure is a major issue for the Biocides and the ECB hosted an OECD workshop on environmental exposure to wood preservatives. Furthermore, the ECB was the Commission's representative in the Biocides environmental exposure project. Similar projects were launched for the human exposure.

An integral part of the support to the review regulation is a well functioning data base support. In this context, a first version of IUCLID for Biocides was finalized.

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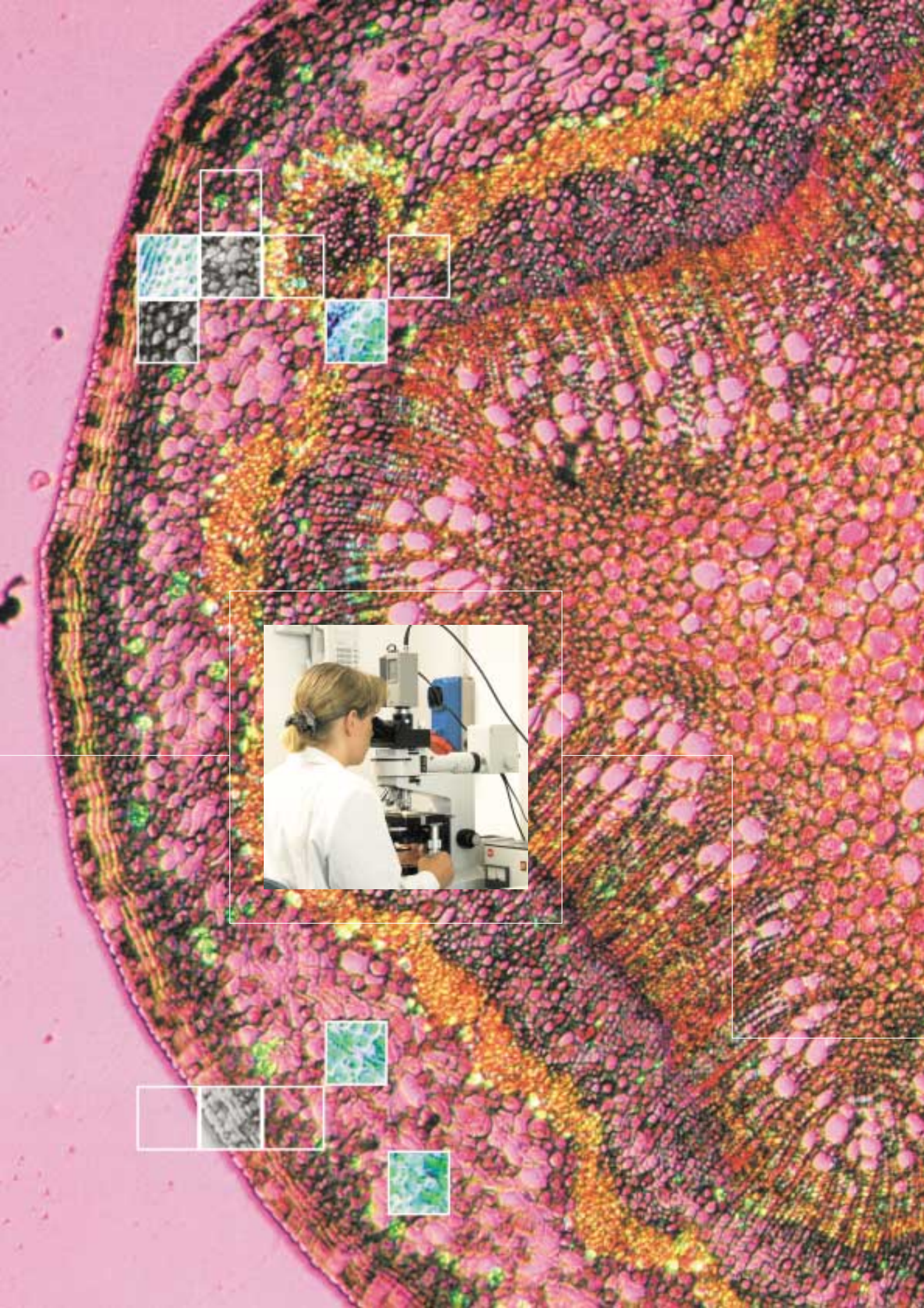

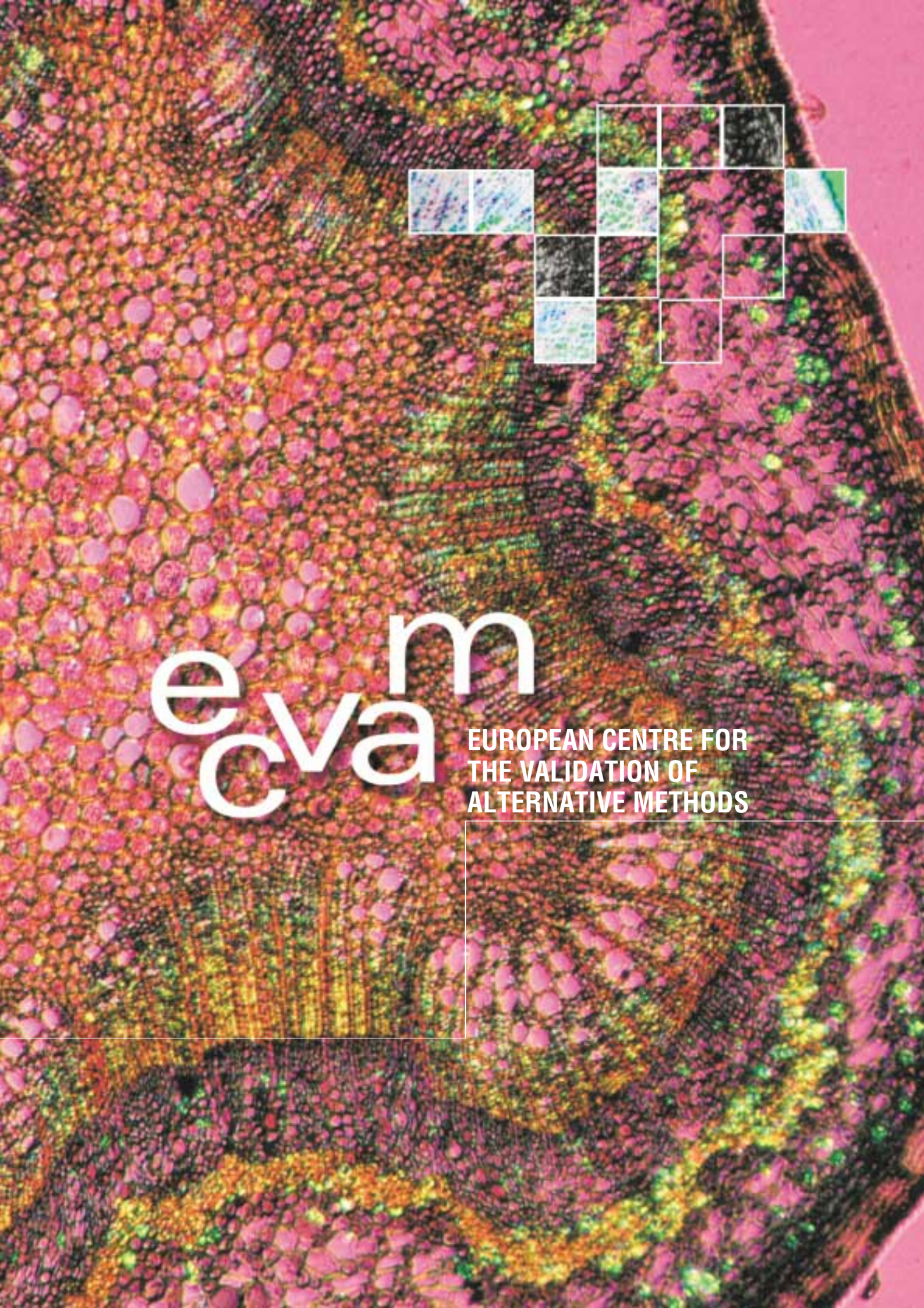
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**Web Information resources**

**At IHCP site:**
*http://ihcp.jrc.it/TheIHCP/Activities/ACTVali.html*

**ECVAM – Scientific Information Services (SIS)**
*http://ecvam-sis.cec.eu.int/*

# European Centre for the Validation of Alternative Methods

## The Validation of Alternative Biomedical Test methods

The European Centre for the Validation of Alternative Methods (ECVAM) is an international reference centre for the independent evaluation of the reliability and relevance (i.e. the validity) of scientifically advanced methods for predicting particular kinds of toxic hazard and for quality control and safety assessment.

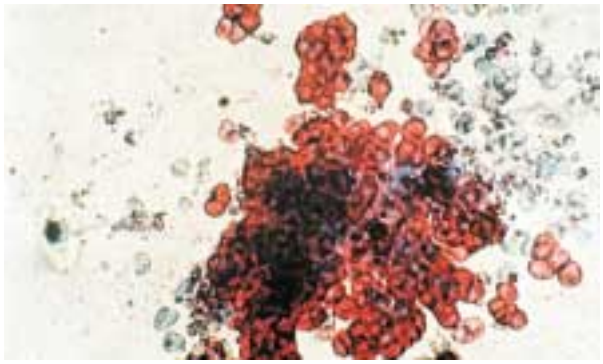
The emphasis is on test procedures, test batteries and integrated testing schemes, which could reduce, and eventually replace the need for tests on laboratory animals.

This involves the development and evaluation of in *vitro* methods (cell and tissue cultures), and the use of computer modelling based on structure-activity relationships and physiological and biokinetic modelling. ECVAM has a wide network of collaborators in academic, industry and government laboratories in the Member States and all over the world and works in close collaboration with DG ENV, DG ENTR, and DG SANCO.

## Validation

Serious decisions must be taken about 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 confirmation that a method has been satisfactorily developed to meet certain criteria, and a prevalidation stage to assure that an optimised 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 the ECVAM Scientific Advisory Committee – ESAC), then consideration by the appropriate regulatory bodies in the Commission and the Member States.

June 2000 was a historic month for alternative methods, since three in vitro methods (two for skin corrosivity and one for phototoxic potential), validated in studies sponsored or managed by ECVAM, were accepted by the EU Member States as Annex V test guidelines in relation to Directive 67/548/EEC. Meanwhile, the ESAC endorsed the local lymph node assay for skin sensitisation, the EpiDerm and Corrositex skin corrosivity tests and two in vitro tests for tetanus vaccines for human use as scientifically validated methods, and ECVAM formal validation studies showed that three in vitro tests for embryotoxicity and an in vitro test for acute neutropenia had met the validation criteria.



## Metabolism and Neurotoxicity

Many chemicals which enter the body are metabolically modified, especially in the liver, to produce more toxic or less toxic compounds. Anticipation of such metabolism and an evaluation of its possible effects is a vital part of pre-clinical studies on drug metabolism.

A prototype for an innovative medium throughput HPLC/MS system for measuring metabolism related enzyme activities has been developed at ECVAM. Two grantholders, associated with this task, obtained their PhDs at the universities of Konstanz and Nottingham. The first attempt to apply a JRC patented system involving genetically engineered neuronal cell lines led to an award for the ApomenCellCheck Kit.

## Reprotoxicity and Cardiotoxicity

The potential of chemicals and products to damage the developing embryo and foetus is a major problem. The successful results of prevalidation/validation studies on the subject, and the related publication in ATLA (Alternatives to Laboratory Animals) in 1999, resulted in 2000 in an award for the best paper of the year.

The same working group was involved in the successful validation of the embryonic stem cell (ESC) test. In this test, embryonic bodies are created *in vitro*, which are composed of beating cardiac cells, haematopoietic cells, muscle cells or nerve cells. The ability of chemicals to affect the differentiation of cells derived from ESC along specific pathways can thus be evaluated. Research at ECVAM is focused on the production of genetically ESCs, in order to develop an effective high-throughput system, and on the development of more sophisticated endpoints to provide answers to mechanistically relevant questions.

## Metal Toxicity

Trace metals and their compounds play a crucial role in many biological systems, and their possible harmful effects (induction of toxic, mutagenic and carcinogenic effects) are addressed in a series of Directives (80/778, 80/1107, 87/416, 89/458, 91/441), which define the limits for the daily intake for trace metals present in the environment and for threshold limit values in the workplace.

An external contract has been awarded for the development of a test for metal induced infertility and spermiotoxicity and active collaboration has been established with other task groups, on the absorption of metals by Caco-2 cells (an *in vitro* model of intestinal absorption) on the embryotoxicity of metals.

## 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. Modifications to these barriers can result in exposure to various types of 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.

The Tecnomouse system for long-term studies *in vitro* has been successfully transferred to ECVAM by contract, thus permitting long term chronic toxicity studies on cells which can be maintained for months without subculturing.

A multi-system for transepithelial resistance has been optimized and has been used in the development of screening procedures for the rapid and reliable detection of toxic effects induced in the renal epithelium by chemicals.

HPLC and luminescence methods for nucleotide measurements have been developed in-house and optimized, as a basis for defining new test endpoints.

Activities concerned with uptake across the intestinal barrier focused on the use of CaCo-2 cell line, in collaboration with various external collaborators, and an external contract was awarded in 2000.

## Haematotoxicity and Anti-Cancer Drugs

The bone marrow, a major part of the blood forming system, is the target for a wide variety of industrial and environmental chemicals, and damage to blood cell formation is a major side effect of anticancer drugs. The availability of *in vitro* testing for evaluating the consequences of exposure to medicines or other chemicals substances in the various blood-cell lineages is sought for within the frame of ECVAM's activities.

The final report on the successful validation studies on the CFU-GM clonogenic *in vitro* test for acute neutropenia is being prepared for publication. The first stage of a study on the prevalidation of the CFU-MK *in vitro* assay for the prediction of thrombocytopenia has been completed.

An evaluation of techniques for the use of human bone-marrow cells as precursors for blood cell lines has taken place, and a number of techniques have been refined. Standard operating procedures for the use of human cord blood cells in clonogenic assays have been produced.

## Biologicals

Biologicals are products such as vaccines, immunosera, immunoglobulins, hormones, monoclonal and polyclonal antibodies. The quality control and safety testing of biologicals still require the use of large numbers of animals; even though some advanced *in vitro* tests already exist for some of these purposes. ECVAM is a partner in or sponsor of a number of prevalidation and validation studies on methods for the quality control of immunobiological and hormones.

The scientific validity of methods for tetanus vaccines for human use was endorsed at the December 2000 ESAC meeting. The report of ECVAM Workshop 41 (ATLA 28, 241-258, 2000) on *Three RS approaches in the production and quality control of avian vaccines*, is already having a very significant effect at the European regulatory level.

## Computer modelling

Computer based systems for predicting toxic effects are of increasing value and significance. Structure-activity relationships (SAR) have been developed to predict the potential of chemicals to cause skin corrosion, eye irritancy, acute neurotoxicity, etc.: an important contribution to the derivation of SAR for predicting the corneal permeability of chemicals and pharmaceuticals has been published in 2000. Interaction with other groups has led to the improvement of a number of prediction models, e.g. in embryotoxicity and cardiotoxicity testing. A Ph.D. was gained at John Moores University, Liverpool.

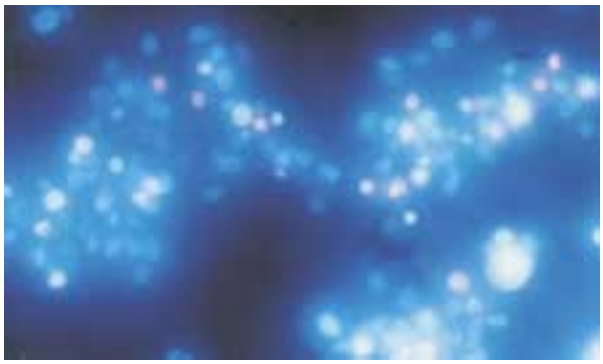
## Biostatistics and Experimental design

The highest possible standards of experimental design, and independent data retrieval and analysis, are crucial to ECVAM's work as a recognized validation agency. ECVAM's biostatistics task force has been re-formed and ECVAM's role is being supported more strongly. An external contract for a review of statistical methods application to prevalidation/validation studies has been awarded. A PhD on evaluation of research involving transgenic animals was gained at the University of Nottingham.

## The ECVAM Scientific Information Service (SIS)

In 1996, a unique scientific information service (SIS) was established to disseminate information (factual and evaluated) on advanced alternative methods for toxicology assessment. It provides full method descriptions, including their development and validation status. Furthermore, detailed protocols for their use, test compounds to which they have been applied, and test results and information on user laboratories are made available.

Selected databases have been prepared for online distribution via the Internet. Furthermore, the total information content of SIS is being updated, with the definition of data sheets on reproductive toxicity, hepatotoxicity, metabolism-mediated toxicity and percutaneous absorption, as well as with the definition and entry of new protocols. An international ESAC subcommittee, created especially for SIS, met for the first time in December and reported the progress, made to the ESAC. A preliminary version of the thesaurus on alternative methods, a project of the ECVAM Task Force on databases, has circulated for comments.



## Cosmetics and Human Volunteer Studies

An external contract is being awarded to provide standardized protocols for the safe and ethical use of non-invasive measurements in human volunteer studies, as a basis for comparing *in vitro* tests and human in vivo test data.

## Shared Cost Actions

Comparison and Validation of Novel Pyrogen Tests Based on the Human Fever Reaction Pyrogen testing is a crucial aspect of the control of medicinal products, as well as of innovative high-tech products such as cellular therapies and species-specific agents (e.g. recombinant proteins). For biologicals, especially blood-derived drugs, a rabbit test still represents the method of choice, requiring hundreds of thousands animals in the EU per year. This test is laborious, expensive, raises ethical concerns and cannot be applied for some of the new products. In recent years, in Europe, a number of alternative cellular assays have been developed, exploiting the human fever reaction. The network brings together the most prominent test systems for trans-national comparison and subsequent validation of the most promising models.

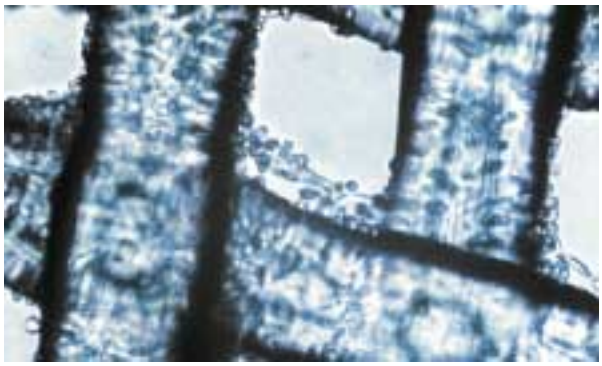
The Innovative Project Competition launched in July 2000 by the Co-operation Strategy and Technology Transfer Unit for JRC researchers, led to an award for the ApomenCellCheck project. The project on the optimization of genetically engineered cell lines for the identification of apoptosis-mediated neurotoxicity, aims to design and develop a test kit (Apomen Cell Check), which can screen in a fast, reliable and technologically and mechanistically relevant manner, for apoptosis-mediated neurotoxic effects. The project embodies elements of technology transfer to industry.

## Other

A management manual has been produced as a day-to-day working guide for all ECVAM staff, incorporating elements such as Good Laboratory Practice, Good Cell Culture Practice, QA, Safety and Project Management.

The 1800 page proceedings of the *3rd World Congress on Alternatives and Animal Use in the Life Sciences* (Bologna 1999) were published in October 2000 by Elsevier BV, Amsterdam.

In the frame of the PECO projects, ECVAM has received funds for the promotion of advanced and alternative testing methods, including development and application, throughout, and in collaboration, with the candidate countries. The programme is already being implemented. Training days, short permanence periods and workshops conferences to be hosted in candidate countries and at the IHCP are envisaged.



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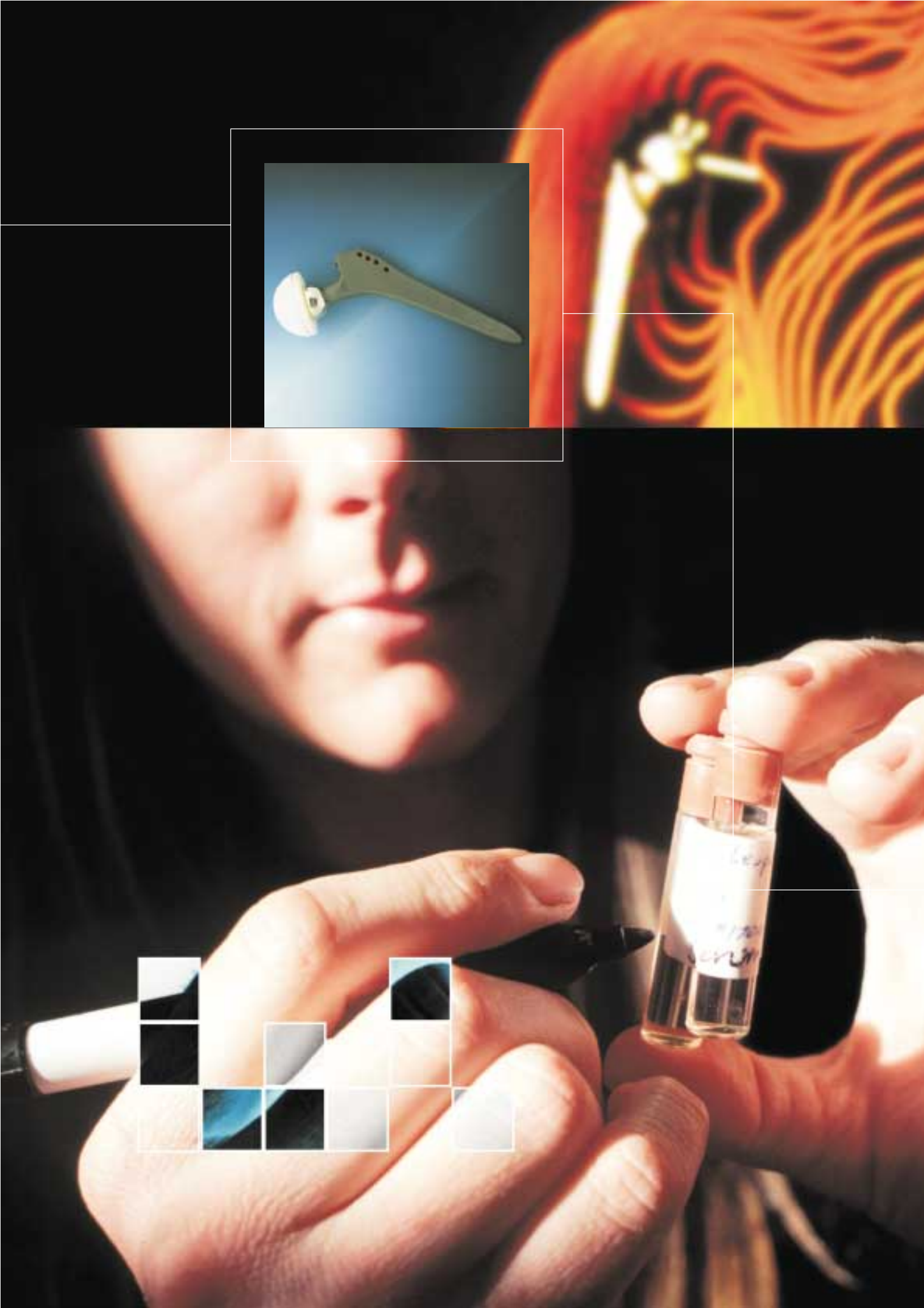

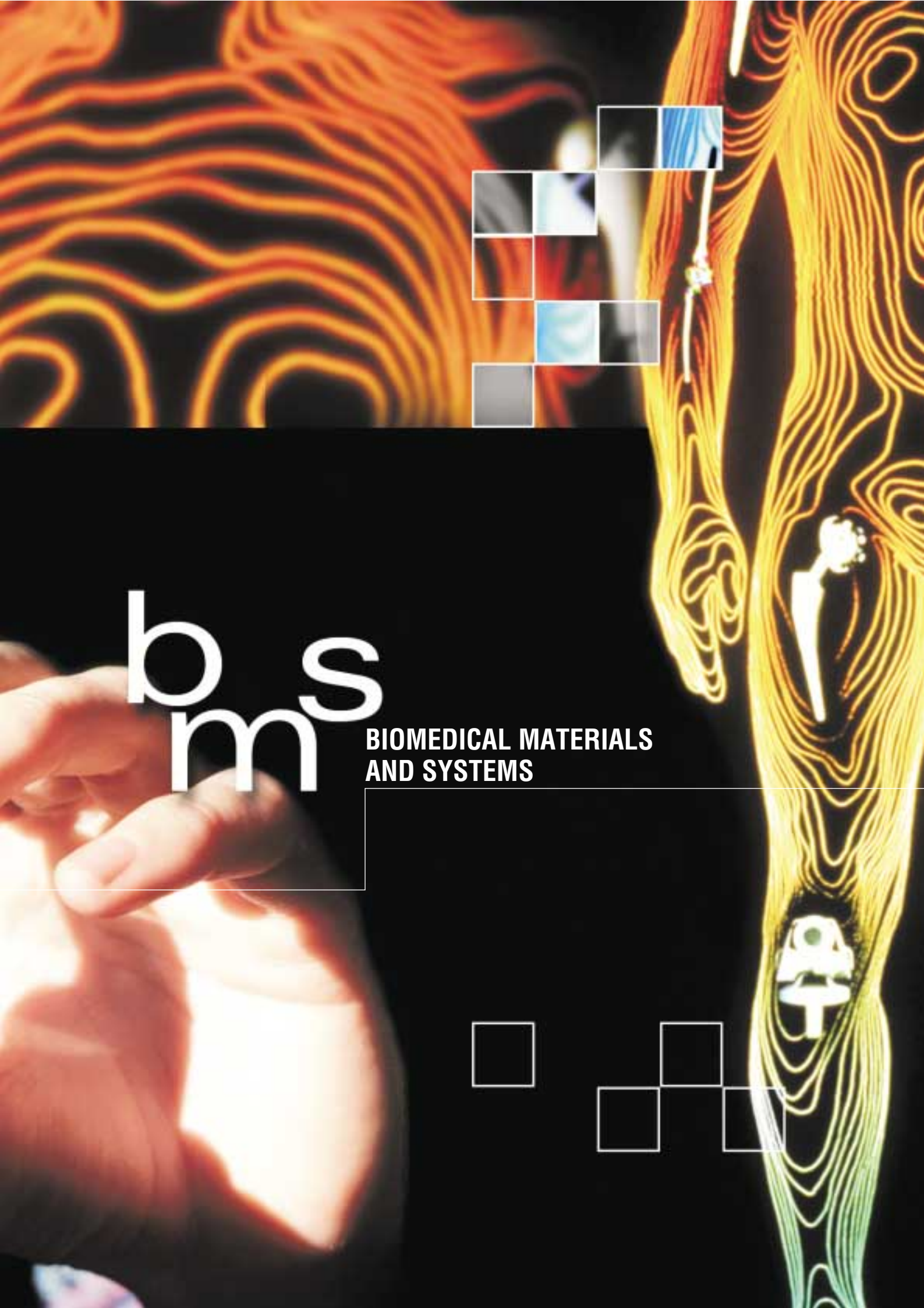
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BIOMEDICAL MATERIALS
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*http://ihcp.jrc.it/TheIHCP/Activities/ACTRadi.html*

# Biomedical Materials and Systems

The Biomedical Materials and Systems (BMS) Unit groups experts in material science, surface engineering, nuclear and optical techniques, applicable to a broad range of health related issues, in particular in the areas of biocompatible implants, medical imaging 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.

Specifically, the work in these areas encompasses the following main priorities:

- Performance testing of biomedical devices in support of harmonization of test methodologies on release from and performance of orthopaedic and dental implant materials and medical devices under clinically relevant conditions using a combination of advanced techniques, in support of Directive 93/42/EEC. Functional materials and systems, involving the development and characterization of biocompatible and bioactive surfaces to improve haemocompatibility of cardiovascular grafts, stents, catheters, and osteointegration of hip and knee replacement prostheses.

- Minimally invasive medical systems including nuclear and optical imaging techniques. This involves, amongst other activities, the contribution to the development of standards for the distribution of radiotracers, and the participation in European Networks.

*Highlight:*

*Installation of the Fluorodeoxyglucose (FDG) production facility at the Cyclotron premises. The module, complete with target, synthesis module, quality control unit can deliver about 40 GBq at the end of each run. Clean rooms (class C and B) are also available for handling the tracers and to comply with GMP guidelines related to radio pharmaceutical production.*

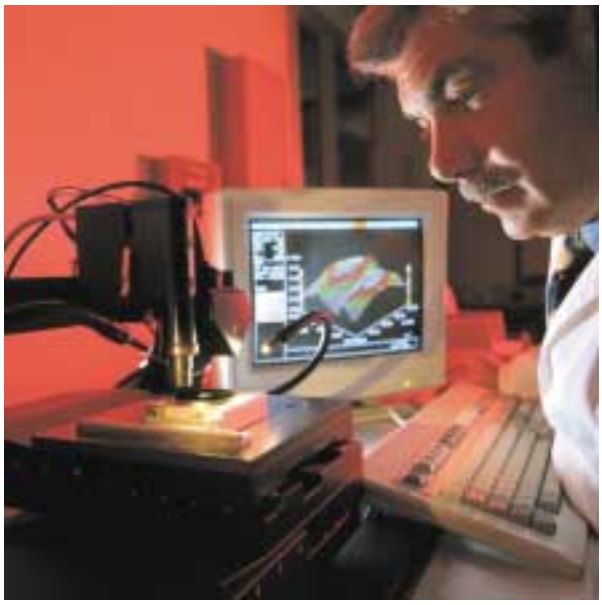
Additional 2000 highlights:

- Launch of the European Thematic Network for Optical Methods of Medical Diagnosis and Monitoring of Diseases (MEDPHOT).

- Pre-normative research in support of the Nickel Directive 94/27 was carried out; with the definition and publication of selected test methods (EN 12472) being adopted by the European Committee for the Standardization (CEN).

- A novel plasma source has been developed to allow PVD deposition of biocompatible films inside tubes, for example catheters.

- During the year it has been decided to phase out the activities on release from consumer products and to concentrate the activities on biomaterials, as described above. Reorganization and prioritization of activites led to a new project structure with 2 major project lines: Reliability of Biomedical Devices and Minimally Invasive Medical Systems.



## Reliability of Biomedical Devices

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.) and 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., Enterprise DG, Health and Consumer Protection DG) 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" (REMED 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 tooth surfaces, and to define improved or new strategies for their safe use while ensuring adequate long term operation.

Carbon thin films have been deposited with a Microwave Assisted PVD reactor (financed by Competitive Support programme of DGXII: project IRDEC). The reactor has been intensively tested and carbon films with a controllable diamond character have been deposited. Biocompatible diamond-like carbon films are deposited on NiTi alloys used in stents, bone sutures and orthodontic appliances as protective coatings to avoid nickel migration.

Nacre coatings have been considered for biomedical implants in the framework of a competitive action. Nacre is a compound found in nature on the inner surfaces of oyster shells. 3 different types of nacre coatings have been Plasma sprayed on several substrates as well as hip joints and dental implants. Osteoblast cells have been grown on the ceramic before and after spraying, as well as Titanium and PE sheets. Results demonstrate the osteoinductive property of the nacre before spraying and after spraying. The clear advantage of the coatings over pure Titanium opens a new route for development of biocompatible coatings.

A biocompatible surface can be obtained by covalent immobilisation of proteins 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. We have deposited a functional film by plasma polymerisation of acrylic acid vapour using an inductive plasma source. Preliminary results 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. Another aspect of the work was the development of a plasma source configuration for treatment of catheters, in which a Transverse Flux plasma source has been tested and patented.

### Performance Testing

Testing of implants under conditions that simulate the specific clinical use (e.g. under realistic dynamic loads, or in the presence of biological liquids for prolonged periods of time) is a key issue in validation of lifetime assessment models and verification of the reliable performance of biomedical devices. Pre-normative test development is needed to identify and evaluate the relevant parameters to be considered by regulators and Industry for standardisation and to allow the qualification of new developments in the field such as the use of new materials, including coatings. An additional requirement is the need to ensure the long-term integrity of the implants, taking into account potentially harmful material release, likely to cause toxic effects in the human body.

In support of Directive 93/42/EEC, pre-normative testing for hip and knee implants was undertaken at the IHCP. Development of pre-normative testing methods, including the effect of different biological lubricants on wear and corrosion, has been pursued.

A 2-axis dynamic loading 3-station hip joint simulator, suitable for pre-normative research, was developed and constructed. Test programmes with up to 3 million simulated walking cycles were performed. Preliminary comparisons with various screening wear facilities indicate that the ranking of materials tested with a simple screening wear facility can be very different from that tested with the simulator. For highly sensitive on-line monitoring of wear, Thin Layer Activation (TLA) was employed. In view of ISO TR9326, regarding the use of TLA for wear of polymers, a collaborative study on possible radiation damage in various medical grade polymers was performed. The feasibility of the use of a special TLA technique for these types of materials was proven. Considering biological effects of wear particles, procedures for isolation of wear particles from biological solutions after testing are being developed in collaboration with ECVAM.

In view of the increasing number of clinical cases reporting metal allergies related to implants and the significant difficulties to determine small amounts of released metal, the use of TLA was further improved. Preliminary results indicate that detection limits can be sufficiently low even in complex biological environments. Thus the method can serve as a reference for conventional methods. A special activation technique to improve the sensitivity by a factor 10 is presently under development. The electrochemical test facilities were complemented with the installation of a scanning reference electrode device, enabling the study of local corrosion phenomena. Due to the increasing interest of surface treatments for potential application in medical implants, some systems were included in wear testing and electrochemical characterisation, including alumina layers and functionally graded ceramic materials (2 related SCAs).

The IHCP carries out research on release due to surface degradation of materials and devices under practically relevant conditions, using a combination of advanced techniques. In particular, highly sensitive electrochemical and nuclear (i.e. radio-tracer) analytical methods can be applied to measure the release of compounds during simulation of practical use. These studies are aimed at providing reference measurements to be used in benchmarking tasks, for instance, to qualify analytic chemistry methods on its progression towards validation studies.

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) being used in orthodontic applications; the varying clinical conditions during use and the absence of reference test procedures. An activity has been initiated on the release of dental systems. Emphasis will be on coupling of dissimilar materials. The feasibility of using radiotracers to measure the release of certain elements was studied. This also forms part of a follow-up of a DG Enterprise ad hoc committee on dental amalgams.

A feasibility study was done for the establishment of a register for prosthetic devices and surgical techniques. The main scope is to collect data on surgery and follow-up of implants from the pre- and post-operative situation and to set up a data bank, allowing a statistical analysis of the performance of different types of prosthesis and surgical techniques. This work will be continued in future in coordination with DG SANCO. It supports the harmonisation of databases on the reliability of medical devices, as a first step towards the establishment of European registers of implants.

### Minimally Invasive Medical Systems

Minimally invasive medical systems are being developed based on radioisotope and optical methods. Radiotracers will play an increasingly important role in medical diagnosis and therapy. As a diagnostic tool they enable the imaging of physiological tissue functions and reveal possible malignant alterations. This functional imaging uses radionuclide-labelled biomolecules that are involved in the metabolism of the tissue under examination. The radiation emitted by the label can be detected outside the body and is used to image the distribution and intensity of physiological processes. Positron Emission Tomography (PET) obtains the highest resolution and accuracy.

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.

The BMS Unit has initiated activities in these areas in the 5$^{th}$ Framework Programme under the work programme Medical Imaging and Therapy using Radiotracers (MIMES). The programme encompasses several tasks, including the production of medical radioisotopes, support for their use in cancer therapies, and the validation of methods applied in medical imaging.

The technical issues in medical imaging concern protocols and guidelines for data acquisition and analysis, which have to be optimized to assure the highest quality of the final examination and reproducibility and reliability of the results. This applies to imaging with PET in particular for the development, implementation and validation of models of tracer kinetics, which aim at a reduction of the time, required for PET scans and an optimization of the sensitivity. Similar issues are important in the field of optical methods for medical diagnosis, which use laser light for morphological and functional imaging.

The production of radioisotopes for research is performed in collaboration with universities, hospitals and other research centres. Commercial production aims at acquiring practical knowledge in the field of quality control at all stages of production and on the technical issues of the distribution and delivery of short-lived radioisotopes to hospitals and research organizations. This knowledge is of strategic importance, given the lack of Europe-wide regulations for the production and distribution of PET radiopharmaceuticals, which hinders the development of a common market and the distribution of PET facilities in clinical centres without their own cyclotrons. Such technical issues must be considered for future European regulations on radiopharmaceuticals. For this purpose, contacts have been established with the European Agency for the Evaluation of Medicinal Products (EMEA) in order to clarify the legal aspects for the production and distribution of radiopharmaceuticals.

In order to establish a programme for anti-cancer therapy using $\alpha$-emitting radioisotopes, studies of the evaluation of interest and resources have been performed. In particular, the IHCP reviewed the current state of the art in production technologies for $^{211}$At. An improved target for $^{211}$At production has been constructed and is being produced. The new target is expected to allow efficient $^{211}$At production at high $\alpha$-pitch current to produce relevant quantities for cancer therapy research.

The production of $^{123}$I for diagnostic purposes has been continued at the IHCP cyclotron in 2000 as Third Party Work. The installation of the target and the production module for FDG (2-deoxy-2[$^{18}$F]-fluoro-D-glucose) was finished in December 2000 and the module can start delivering about 40 GBq of FDG at the end of each run, starting in January 2001.

The use of laser light enables morphological and functional imaging *in vivo* as well as non-invasive or minimally invasive therapeutic techniques. The work in 2000 resulted in the establishment of a partnership leading to a European Thematic Network dealing with "Optical Methods for Medical Diagnosis and Monitoring of Diseases" with IHCP-BMS as network manager. Mathematical methods which had been developed at the JRC in the context of studies on reactor safety, radiation shielding and light transport in air-water systems have been reviewed and work has been started on the conversion of existing computer codes for the description of light propagation in biological tissue. This allows the improvement of computer models for the optical characterization of biological tissue based on Monte Carlo Simulations and Diffusion Theory.

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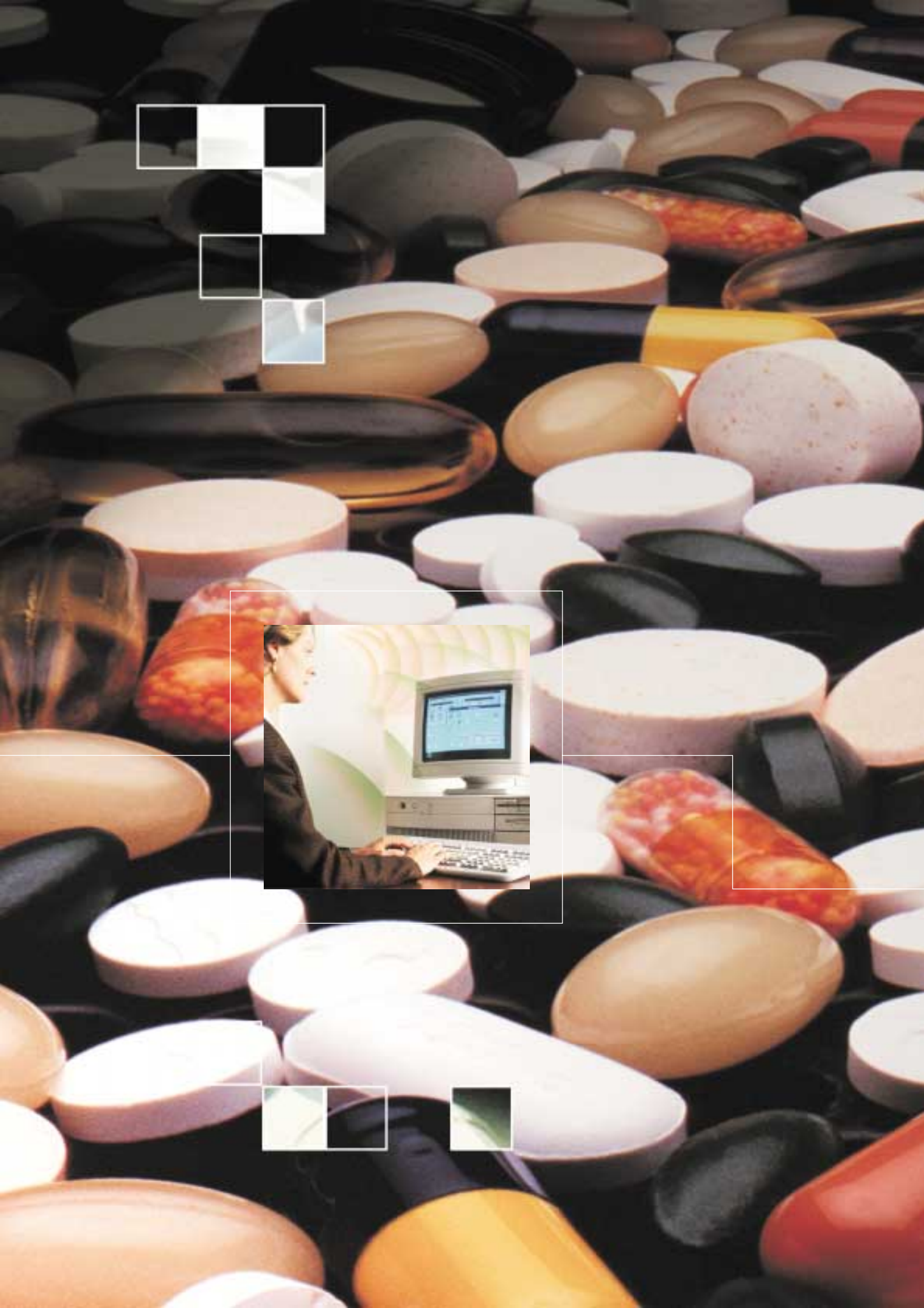

# SUPPORT TO PHARMACEUTICAL RESEARCH

**Web Information resources**

**At IHCP site:**
*http://ihcp.jrc.it/TheIHCP/Activities/ACTPhar.html*

# Support to Pharmaceutical Research

## Telematic systems for the EU Pharmaceutical regulatory activity

The regulatory procedures necessary to assure efficacy and safety of medicines (including vaccines, blood derivatives, radiopharmaceuticals etc.) require a combination of information/communication systems to support the essential Europe wide co-operation.

IHCP is a well-established R&D provider for the study and development of these information/communication tools (including data models and application protocols). The work is carried out in collaboration with DG ENTR, 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: the Eudratrack Mutual Recognition (EMR- developed taking advantage of the EudraNET network, adopted by all pharmaceutical and veterinary authorities) supporting decentralised applications and the EudraNet services supporting authorization for the entire market and post-market control.

In the current workprogramme, IHCP is pursuing the upgrade of the EudraNet network, incorporating advanced network services (such as EudraSafe) and the development of a Unified Tracking System (UTS), integrating both marketing authorization procedures and EMR and primary tracking systems (ATS) in order to track all types of marketing authorization procedures and to monitor improper submission. The implementation of an information dissemination application (Medicines Information Network for Europe – MINE) based on a central database on all authorised medicinal products is also pursued.

All these new services focus on secure communication over the public network, including the document delivery and the distributed co-operative environment among EMEA, the Commission services and the National Authorities, assigning the JRC a central role as data manager of the EU portal for all authorized medicinal products on the market.

Taking into account the objectives to be pursued, the need for focussing the IHCP activities and increasing requests from customers, it has been decided to cancel all activities running in the Unit (e.g. on electronic commerce etc.) except those in support of the pharmaceutical regulations, re-allocating all resources accordingly.

## EudraTrack Mutual Recognition (EMR) system

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 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), which then 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. EMR contains a number of services to facilitate retrieval and dissemination of information, including reporting, alerting and query system as well as e-mail generation. It handles about 350 new events each day. In 2000 the system was upgraded with faster query tools.

In addition, the TSE issue has been considered.

## Unified Tracking System (UTS)

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. The first prototype was presented in 1999, allowing UTS users to trace the processes of authorization and evaluation of medicinal products. In 2000, a new classification into five levels of 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 the contents of the following fields (e.g. CMSs, MA holder, Product name, Active substances, Pharmaceutical form, ATC code and RMS contact).

## Medicine Information Network for Europe (MINE1)

MINE is a network-based application which aims to establish a coherent, comprehensive European Data Centre to provide official information about human and veterinary medicinal products authorized in the EU in accordance with Council Regulation No. 2309/93. it offers structured and standardized information about the efficacy and safety of medicinal products marketed in the EU. The medicinal product database, complemented with the document base providing related official public documentation (EPARs, SPCs, PILs, scientific discussion, etc.), has embedded knowledge that allows intelligent, complex retrieval of information. As soon as the process for collecting all information for all authorization procedures in the UTS database is finalized, the MINE system will become the first European wide socio-economical system dedicated to public health and consumer protection.

## EudraNet Network services

Both UTS and MINE1 services are implemented on top of a new generation of network services offering advanced workgroup collaboration tools such as EudraSafe, which provides the capability of secure transfer of confidential documents between users who are not directly connected to the private EudraNet backbone, but have access to Internet services; DVC (Desktop Video Conferencing); and e-Room, a conferencing and file sharing system. At the same time, studies are underway for the next phase of Eudranet, known as Eudranet 2, which will make use of cryptography based security services to implement a secure data communication network in the form of one or more private tunnels over a public network.

### Publications 2000


V. Pagliari and A. Rana: *"The Unified Tracking System (UTS) - Medicinal Product Data Model"*, Technical Note I.00.142, December 2000.

A. Rana and F. Argentesi: *"Medicine Information Network for Europe: delivering to consumers information about medicinal products authorised in the EU"*, to be presented at the *"eHealth: a Futurescope" the 3rd International Conference on Advances in the Delivery of Care*, London, April 4–6, 2001.

S. Sanfelici, A. Rana: *"A survey on Electronic Payment Systems"*, Special Publication No. I.00.88, June 2000.

V.Pagliari and C. Bartolini: *"EudraTrack Mutual Recognition – User's Manual – version 5.2.16"*, Special Publication No I.01.20.


### Specific events

Training Course provided to EudraTrack users, held in London - June 19-21 and June 27-28.

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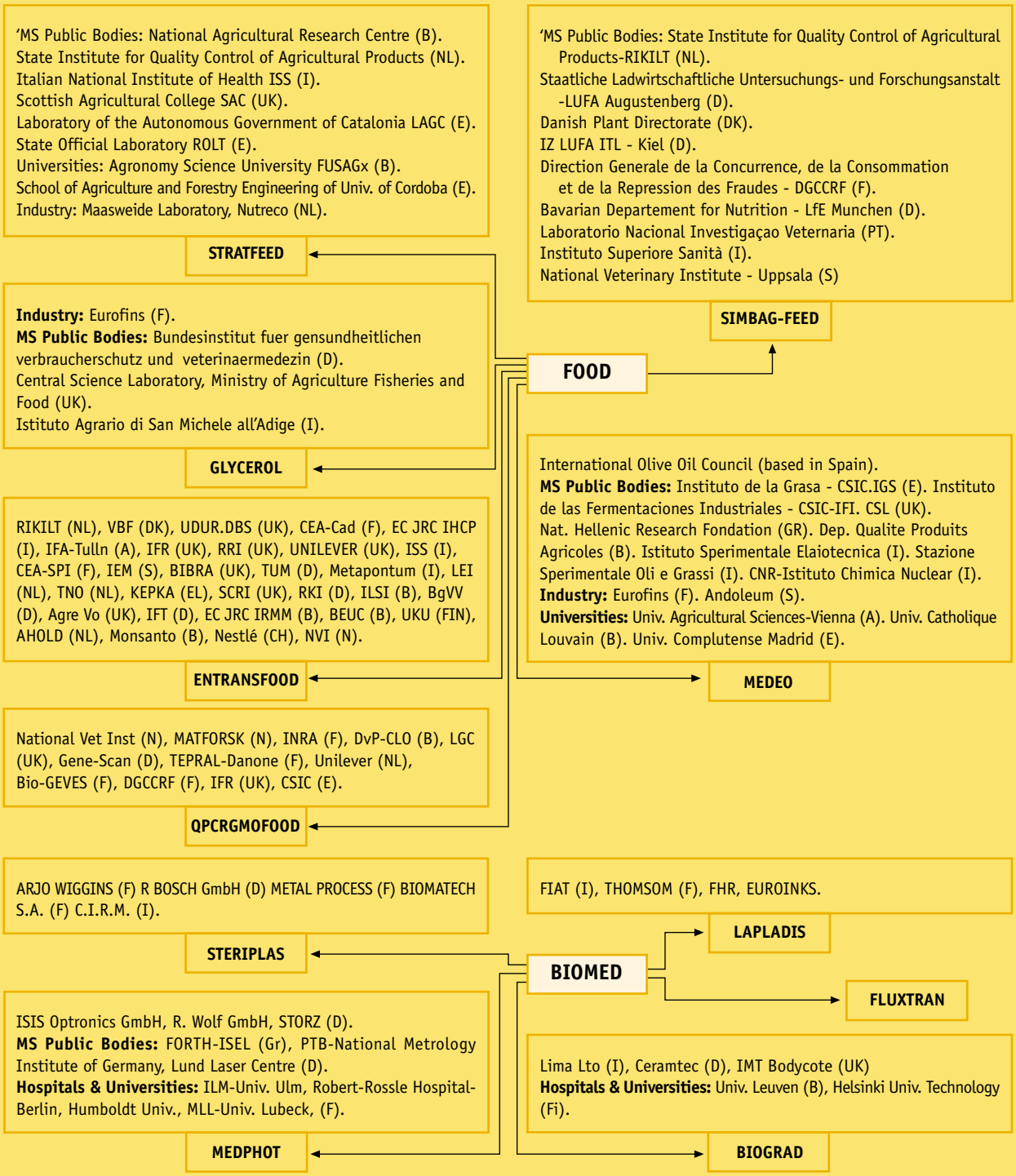
# Networking - Examples




# 2000 Performance Indicators

**RELEVANCE:** Link with policy legislation.

**COSTUMER FOCUS:** **Results of survey** among DGs (performed in 2000) • "excellent" evaluation about results provided by IHCP and its impact.
**Emergency reactions:** • animal feed ban • phthalates.
Both cases have shown a very fast and effective response to "crisis" situation.

**NETWORKING/COLLABORATIONS/PARTNERSHIP:** • Leader in the GMO networks • New SCA started (6 actions formalised, 5 on going) • Coordination for the animal feed ban • Increase of the ECVAM network base.

**TRAINING (given):** • 4 courses in GMO for WHO (letter of appreciation received) • 2 ECB courses on IUCLID • People from candidate countries on GLP (3 persons, short stays at ECVAM).

**PUBLICATIONS:** • Monographs/Periodicals: 72 • EUR: 10 • Conferences: 108 • Special Publications: 21.

**PRIZES/AWARDS:** • 1 award for micotoxins • 2 innovative projects • 6 SCA • 1 recognition for TLC method; 1 award for alternatives.

**PATENTS:** • 14 since 1998

European Commission

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