INSTITUTE FOR HEALTH AND CONSUMER PROTECTION

ACTIVITY REPORT 2003

EUROPEAN COMMISSION
DIRECTORATE-GENERAL
Joint Research Centre

Report EUR 21198 EN

Institute for Health and Consumer Protection

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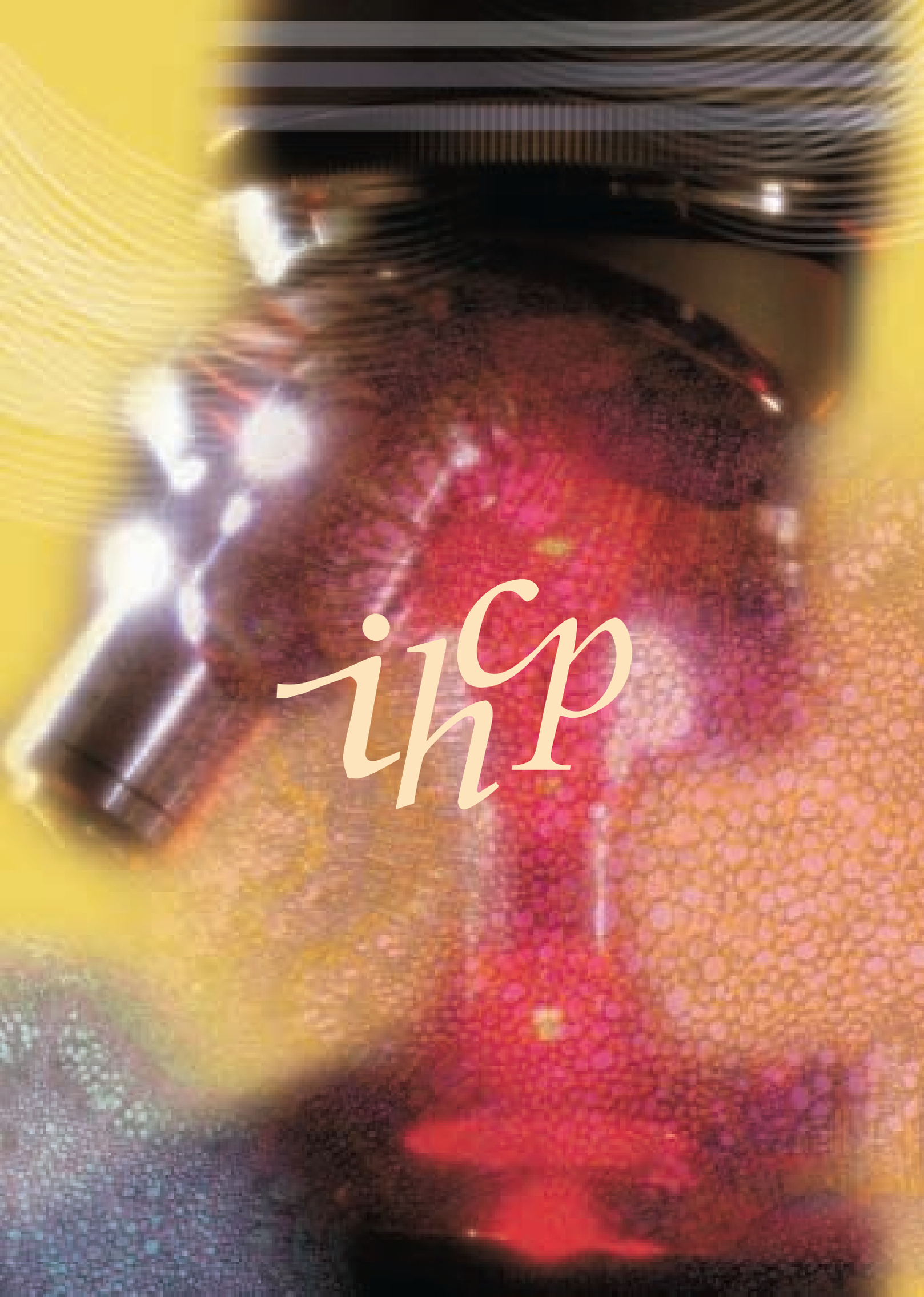
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Foreword

The IHCP was established in October 1998 through the reorganization of existing expertise and structures within the JRC Institutes in the area of health and consumer protection. On January 15 2002 I had the pleasure and honour to take up my duties as Director of this Institute. The biggest challenge since then was to position the IHCP as a scientific reference and validation centre that translates scientific knowledge into a real support for the policy-makers. Looking back, I am proud to say that it has taken up this role in many of its scientific areas. For example the IHCP has played a central role in the drafting of the new chemicals legislation through provision of expertise in risk assessment. Its analysis in 2003 on the additional testing needs under the new EU Chemicals Policy (REACH) has lead to increased awareness among Member States and industry that refined exposure information, cell culture tests and computer models, such as quantitative structure activity relationships (QSARS), can lead to a significant reduction of direct testing costs, the use of animals and speed-up the assessment process. The IHCP has also actively promoted the replacement of laborious and costly laboratory animal tests for the safety evaluation of chemicals with modern alternative methods.

Over the last five years the IHCP has combined its efforts with industry to eliminate existing deficiencies in data on human exposure to chemicals allowing a more accurate evaluation of the overall risk for European citizens when exposed to chemicals from various sources (ingestion, inhalation, skin contact). In 2003 we produced an important report on environmental tobacco smoke (ETS) supporting national legislation to ban smoking in certain public areas.

Besides chemicals, the IHCP gave substantial support in the drafting of new EU Regulations on genetically modified organisms (GMOs) mandating the IHCP to act as the Community Reference Laboratory (CRL), regulating the detection, identification and quantification of genetically modified organisms (GMOs) in food and feed.

The IHCP has actively contributed in shaping the European Research Area through extensive networking, such as the European Network of GMO Laboratories (ENGL) and training of scientists from the Member States and Accession Countries.

April 2004

Kees van Leeuwen
IHCP Director

IHCP Mission Statement

The mission of the IHCP is to provide scientific support to the development and implementation of EU policies related to health and consumer protection. The IHCP carries out research to improve the understanding of potential health risks posed by chemicals, biocides, genetically modified organisms, contaminants released from food contact materials and consumer products.

Scientific Objectives

IHCP activities focus on the following scientific objectives:

- Validation of methods to detect genetically modified organisms (GMOs) in food and feed.
- Development and validation of alternative testing methods to replace, reduce or refine the use of laboratory animals in biomedical sciences.
- Assessment of risks to health and environment from chemical substances, and management of related information service.
- Evaluation and quantification of exposure to environmental stressors (such as chemicals, biological contaminants, radiation and noise).
- Development, validation and use of advanced processing techniques and test methods for the qualification of biocompatible materials, medical devices, and health diagnostics.

End-users/Collaborations

IHCP's direct end-users are services within the European Commission. Moreover, IHCP collaborates with a large number of universities, industrial partners, European and national authorities, international organizations, and consumer associations (the following is a non-exhaustive list):

Customers (within EC)	• DG Agriculture, DG Environment, DG Enterprise, DG Consumer Protection (SANCO), DG Research, DG Trade, DG Taxation and Customs Union (TAXUD), DG Enlargement, European Anti-Fraud Office (OLAF) • DG JRC: EI (Ispra), IRMM (Geel), IAM (Petten), ITU (Karlsruhe), IPTS (Seville) • European Medicine Evaluation Agency (EMEA)
Customers (outside EC)	• European Parliament • International organisations (i.e., OECD, WHO, FAO, Council of Europe, European Directorate for the Quality of Medicines (EDQM)) • Interagency Committee for the Validation of Alternative Methods (ICCVAM) • US Environmental Protection Agency • US Food and Drug Administration • European agencies - Governments (i.e., Competent authorities responsible for the implementation of biotechnology and novel food Directives; chemical authorities, pharmaceutical regulatory agencies in the European Economic Area (EEA), regulatory and health care authorities) • Non-governmental organisations (NGOs) • Industry (i.e., biotechnology, food and feeding stuff, chemicals, cosmetics, biomedical and pharmaceutical) • Consumer Organisations • National Research Institutions and Universities

Executive Summary

In 2003 the IHCP gave significant scientific support to the drafting of new EU Chemicals legislation (REACH), which the Commission proposed on October 29th 2003. In the future it will continue to provide assistance in the implementation of REACH regarding the development of necessary guidance documents, software tools and infrastructure. This support is based in particular on the work of the European Chemicals Bureau (ECB) with respect to data collection, priority setting and risk assessment of existing chemical substances and on its coordinating role of the EU notification scheme and risk assessment for new chemical substances. In 2003, 400 new substances were notified and 30 risk assessment reports on existing substances were produced. 5 testing methods were submitted for Annex 5 of Directive 67/548/EEC, which contains binding EU standardised testing methods to determine hazardous properties of chemicals. A large part of the ECB's work in the past few years is related to the technical and scientific support needed for the development, introduction and adaptation of testing methods of Annex V to Directive 67/548/EEC. In 2003 the ECB prepared a list of 250 classified and labelled substances, which will be part of the next Adaptation of the Directive 67/548/EEC.

Following an administrative arrangement between DG TAXUD and the JRC, the ECB is currently carrying out a feasibility study on the further improvement of the European Customs Inventory of Chemical Substances (ECICS), which allows identification of all marketed chemicals for customs and legal purposes (approx. 28 600 substances). It has established the European Chemical Substances Information System (ESIS, **http://ecb.jrc.it /esis***)*, which offers for the first time a single search tool on chemicals and the legislation under which they are presently covered.

The proposed REACH system foresees the application of alternative methods to the testing of chemicals produced or imported in quantities above 1 ton. To achieve this objective the Commission promotes the use of non-animal testing methods, such as: **(1)** refined exposure information, **(2)** computer models and **(3)** cell culture tests. These new risk assessment strategies are essential for the implementation of REACH and bear the potential to significantly reduce the costs associated with it. Responding to these needs, the IHCP has — in addition to its ongoing activities on cell culture testing and exposure assessment — launched an initiative on computer models, such as Quantitative Structure-Activity Relationships (Q)SARS, to promote their development, validation and implementation for regulatory use. This involves the work of both the European Chemicals Bureau (ECB) and the European Centre for the Validation of Alternative Methods (ECVAM).

ECVAM was established by a Communication of the European Commission and Parliament (SEC/91/1794) to support the implementation of the Directive on animal protection (86/609/EEC). ECVAM is the European reference centre for the independent evaluation of the relevance and reliability of tests for specific purposes (e.g. toxicology assessments of various types of chemicals, quality control and safety assessments of biologicals), through research on advanced methods, new test development and validation, and the operation of specialised databases. 11 key-areas have been established or were reinforced with the support of various working groups with participation of stakeholders and international experts. The activity on the validation of computer models for toxicity assessment, in particular Quantitative Structure Activity Relationships (QSARS), will be enlarged over the coming years to respond to the needs regarding the implementation of REACH. The QSAR Action on the promotion of the development, validation and implementation of (Q)SARs is carried out in close collaboration with the European Chemicals Bureau (ECB).

The IHCP Physical and Chemical Exposure Unit (PCE) was transferred from IES in 2000 and has close links with industry to work together towards eliminating existing deficiencies in data on human exposure to chemicals. This also allows the JRC to evaluate more accurately the overall risk for European citizens when exposed to chemicals from various sources (ingestion, inhalation, skin contact). It provides scientific understanding, information and assessment tools to support the Commission services in evaluating and quantifying human exposure and risk assessments for environmental stressors. Stressors include chemicals, UV-radiation, electromagnetic fields and noise. The overall objective for the PCE Unit is to develop infrastructure, tools and reference data to enable harmonised exposure assessment procedures in the EU, and to support the implementation of key policies and directives, such as the New Chemicals Policy, the General Product Safety and Indoor exposure limits for priority pollutants (INDEX).

The European Union has put in place a set of strict procedures for approving the growth, import and/or use of GMO food or ingredients. EU legislation guarantees the consumer's right to information. Since 1997 labelling to indicate the presence of GMOs as such or in a product is mandatory. However, Regulation (EC) 1830/2003 reinforces the current labelling rules extending mandatory labelling to all food and feed products. In this context traceability provides the ability to trace GMOs and products produced from GMOs at all stages of their placing on the market through the food production and distribution chains. The Biotechnology and GMOs Unit is the JRC reference for the provision of scientific and

technical support to the EC biotechnology regulatory framework and for the development of biotechnology expertise in areas relevant to health and consumer protection. The Unit work focuses on the development and validation of appropriate methods for sampling, detection, identification and quantification of Genetically Modified Organisms (GMOs) in different types of matrices. In the context of Regulation (EC 1829/2003) on genetically modified food and feed, the Joint Research Centre (JRC) of the European Commission and – in particular - the IHCP Biotechnology and GMOs Unit, was appointed as the "Community Reference Laboratory" (CRL). The CRL is assisted in this important task by the European Network of GMO Laboratories (ENGL), coordinated and chaired by the Unit itself, and considered as one of the major achievements of the JRC in recent years. The ENGL constitutes a unique platform for experts from EU Member States to discuss technical issues related to sampling, detection, identification and quantification of GMOs. In support of the Commission policy, the Unit provides specific technical advice and expertise to various Commission Services, such as: the reception of all summary notifications of deliberate field trials (SNIFs), notified under Directive 2001/18/EC and the participation as nominated expert in the development of an operational Biosafety Clearing House.

In the last five years, the BMS-Unit has developed as a horizontal "enabling" technology provider in support of the JRC priority areas for policy related research. The Unit's strength lies in the cross-functional research activities, which are performed in the frame of two institutional Actions on 'Nanobiotechnology for Health Applications' (NBT) and 'Medical Devices and Health Technology' (MEDTECH), which were initiated in the Sixth Framework Programme. The Nanobiotech project opens a complete new research field at the IHCP and JRC, through the development of specific interfaces between biological/non biological systems. First applications are linked to controlled surface structures opening route to high selectivity/highly paralleled analysis systems. The scientific activities in the Action MEDTECH were concentrated on production technologies for medical radioisotopes and materials research. Special emphasis was given to training activities of young researchers including external funding through the Marie-Curie Programme (Joint ECVAM-BMS MC-Training Site, individual MC fellowships).

The IHCP was established in October 1998 through the reorganization of existing expertise and structures within the JRC Institutes in the area of health and consumer protection. Since then the main themes of the IHCP have been food, chemicals and health carried out by five scientific Units. In 2002 a reprioritisation exercise was carried out resulting in the integration of the activities on food products into the Institute for Reference Materials and Measurements (IRMM) in Geel, Belgium, and the termination of the Unit Support to Pharmaceutical Regulation (SPR). In the same year, two new Units were created: "Biotechnology and GMOs" and "Physical and Chemical Exposure (PCE)". Into the latter selected activities from the Institute for Environment and Sustainability (IES) were integrated.

In the following the main achievements of the different scientific Units of the IHCP are summarised.

Food Products and Consumer Goods (part of the IHCP from 1998 to 2002)

The objective of the Food Products and Consumer Goods Unit was to develop, harmonize and validate analytical methods in the areas of food safety, food quality and safety of consumer goods. As a result of a reprioritisation exercise in 2002, this Unit was integrated into the Institute for Reference Materials and Measurements (IRMM) in Geel, Belgium. In 1999 a large part of its work was dedicated to the support to the Belgian Authorities by developing simplified methods for the determination of polychlorinated biphenyls (PCBs), which were the source of dioxin contamination detected in Belgian food and feeds at that time. The emergence of a new variant of Creutzfeld-Jacob disease during the BSE (Bovine spongiforme encephalopathy) epidemic and the subsequent ban on the use of specified risk materials (SRM), led to an activity, in which a method for the detection of central nervous tissue (the main SRM) in meat and bone meal products was developed.

The work in the area of food contact materials focused on the development and validation of methods for the determination and detection of Bisphenol-A-Diglycidylether (BADGE) in certain food products (e.g. canned food), which are able to migrate into food or can react with other compounds in the food or in the food package. A web site containing a list of substances used in materials and articles in contact with food was launched in 1999 (**http://cpf.jrc.it**). Research was also carried out on the migration of Phthalates, which are used as softeners in PVC toys and children's articles. In 2003 DG SANCO proposed to designate the food contact laboratories as a future Community Reference Laboratory (CRL). The use of these substances in toys has been temporarily banned in 1999 (Commission decision 1999 /815/EEC). The activities on food contact materials were integrated into the Unit "Physical and Chemical Exposure (PCE)".

Physical and Chemical Exposure, PCE (created in 2002)

In the frame of activities to evaluate human exposure to environmental tobacco smoke (ETS) components in indoor environments, a series of tests were undertaken in 2003 to investigate the impact of various ventilation rates on the air concentration of ETS-components. The tests were carried out at the European Commission-Joint Research Centre's INDOORTRON facility, a 30 m3 walk-in type environmental chamber.

Preliminary evidence indicates that changes in ventilation rates simulating conditions expected in many residential and commercial environments during smoking do not have a significant influence on the air concentration levels of ETS constituents, e.g. CO, NOx, aromatic compounds, nicotine. This suggests that efforts to reduce ETS originated indoor air pollution through higher ventilation rates in buildings, including residential areas and hospitality venues, would not lead to a meaningful improvement of indoor air quality. Moreover, the results show that "wind tunnel"-like rates or other high rates of dilution ventilation would be expected to be required to achieve pollutant levels close to ambient air limit values.

The work undertaken at the European Office of Wine, Alcohol and Spirit Drinks (BEVABS) ensures effective control of major fraud, such as sugaring and watering in the wine sector. Since 2002 BEVABS forms part of the PCE Unit of the IHCP. One of its core tasks is the management of a database, which contains information on thousands of authentic wines produced in the EU since 1991. This includes results of isotopic analysis, as well as more than 80 additional parameters such as geographical origin, grape type and chemical analysis.

In early 2004, the PCE Unit expects to pass the SINAL audit for the extension and accreditation for the method performed in BEVABS on the analysis of wine, fermented juices, spirit drinks and alcohol and the CERMET audit for the measurements of chemicals emissions from products and articles including human exposure to indoor and occupational environments.

Biotechnology and Genetically Modified Organisms, B&GMOs (created in 2002)

The increasing public debate on genetically modified organisms (GMOs) and their effect on human health and the environment as well as the moratorium for EU approval in 1999 made the activities on GMOs a priority area of the JRC and the IHCP. In 2002 these activities were concentrated in a new Unit of the IHCP "Biotechnology and GMOs" with the objective to provide scientific and technical support for the implementation of EU policy in the area of biotechnology. A major task in 1999 was the establishment of a system for the exchange and analysis of the information within notification files for R&D field trials before being distributed to the Member States' Authorities for approval. Submission of notification dossiers is made using the Commission's Summary Notification Information Format (SNIF). During 2003, the system allowed the circulation of 82 SNIFs regarding deliberate field trials, and 23 SNIFs regarding placing on the market. In the area of detection of GMOs the IHCP was involved in a validation study of GMO material in flour raw materials derived from modified crops (Roundup-Ready®, soybeans and BT-176 maize). The results showed that the PCR (polymerase chain reaction) based method is a suitable screening technique for these specific flours present in various concentrations in their non-GMO counterparts. In order to facilitate and speed up the collection and exchange of information, a "European Network on GMO Laboratories (ENGL)" coordinated by the IHCP was founded in June 2000 upon request from Member States. Four training courses on the analysis of food samples for the presence of Genetically Modified Organisms were held at the IHCP in 2000 in collaboration with the World Health Organization (WHO).

In the context of the European Union GM Food and Feed Legislation a "Community Reference Laboratory (CRL)" has been established at the IHCP. The core task of the CRL is the technical evaluation and validation of quantitative detection methods for GM Food and Feed as part of a Commission authorisation procedure. The Joint Research Centre (JRC) of the European Commission, and — more precisely — the Biotechnology and GMOs Unit, has been given the mandate for the operation of the CRL. It does so in collaboration with a European Network of more than seventy National Control Laboratories, assembled in the European Network of GMO Laboratories (ENGL).

European Chemicals Bureau, ECB

The ECB carries out technical and scientific work needed for the development, introduction and adaptation of testing methods of Annex V to Directive 67/548/EEC. It plays a central role in the establishment of the New EU Chemicals policy (Registration, Evaluation and Authorization of Chemicals, REACH), which the Commission proposed on 29 October 2003 (COM(2003) 644 final). A report "Assessment of Additional testing Needs under REACH" (EUR Report 20863 EN, 2003) was produced by the IHCP concluding that considerable saving can be made on the direct testing costs for chemicals safety assessment if (Q)SARS — (Quantitative) Structure Activity Relationships —, are applied. The IHCP has launched an initiative on estimation techniques that are useful for regulatory purposes, such as (Q)SARS, to promote their development, validation and implementation for regulatory use. This involves the work of both the European Chemicals Bureau (ECB) and the European Centre for the Validation of Alternative Methods (ECVAM). In relation to the implementation of REACH, the JRC anticipates that a certain number of validated (Q)SARs will have to be available by 2006. The (Q)SARS activity was integrated into ECVAM in 2003.

During the last five years the ECB increased its large network of collaborating partners in industry and academia in the member states, and on its track record in successfully training experts on risk assessment tools (the European Union System for Evaluation of Substances, EUSES) and the International Uniform Chemical Information Database IUCLID. In 2003 the ECB established the European Chemical Substances Information System (ESIS, **http://ecb.jrc.it/esis**), which — for the first time — offers a single search tool on chemicals and the legislation under which they are presently covered.

The European Centre for the Validation of Alternative Methods, ECVAM

Together with the ECB, ECVAM plays a key role in the implementation of REACH aiming to minimise the use of experimental animals and to speed up the policy implementation through the development and validation of more cost-effective and faster *in vitro* techniques.

In support to the implementation of the 7th amendment of the cosmetics Directive (Council Directive 2003/15/EC), which foresees phasing out animal experiments within 10 years, ECVAM co-ordinated the creation and operation of several international *ad-hoc* working groups to establish the "state-of-the-art" of alternative methods for human health effects, in support to a jointly established working group of Commission services and stakeholders.

ECVAM conducts research in several areas of toxicology relevant to the safety testing of chemicals of various kinds (including cosmetics and pharmaceuticals). Particular emphasis was given on the establishment of the human embryonic stem cell technology. It has been set up a consortium of about 30 partners to develop *in vitro* tests that can be used as building blocks in future test-

ing strategies with the aim to detect reproductive toxicants. The Integrated Project proposal (ReProTect) has been successfully submitted to DG RTD and it's foreseen to start on the 1st of July 2004. A second Integrated Project, A-Cute-Tox, aiming at developing a replacement strategy for acute toxicity, was selected and is being currently negotiated.

In 2003 the validation study on pyrogenicity testing, guided by ECVAM, was successfully completed. It showed that a few human blood cells are able to eliminate animal testing for parenteral (non-oral) drugs, saving the lives of 200.000 laboratory rabbits per year in Europe.

The JRC hosted the 1st Meeting of the OECD Expert Group on (Q)SARs to develop a proposal for the QSAR activity, which was subsequently adopted by the OECD Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology.

ECVAM's Scientific Information Service (SIS) has been extended to an interactive information service, reaching 2900 registered and active users from 65 countries.

Biomedical Materials and Systems, BMS

In the last five years, the BMS Unit has developed as a horizontal "enabling" technology provider in support of the JRC priority areas for policy related research. The Unit's strength lies in the cross-functional research activities, which are performed in the frame of two institutional Actions on 'Nanobiotechnology for Health Applications' (NBT) and 'Medical Devices and Health Technology' (MEDTECH), which were initiated in FP6.

The activities in NBT regarding the development of new biosensors and advanced methods for the detection of toxicological endpoints are centred in one of the most promising and rapidly expanding fields of current research being highly relevant for the scientific-technological underpinning of toxicity testing required by the REACH legislation and in the emerging priority area of Environment and Health. The competencies in these areas were developed from long standing experience in plasma surface processing and surface characterisation.

Prenormative research in support to the Nickel Directive 94/97 was carried out with the definition and publication of selected test methods, which were adopted by the European Committee for Standardisation (CEN). An orthopaedic implant testing laboratory was set up with a range of wear testing facilities (screening devices and hip/knee joint simulators) to improve and harmonize wear test methods for hip and knee prostheses in support to Directive 93/44/EEC including methods for the characterization of ceramic and polyethylene wear debris.

The MEDTECH Action covers the cyclotron activities and deals with radioisotope production for research use. The focus lies on new production technologies of novel biomedical radioisotopes for diagnostic and therapeutic applications.

BMS Unit, together with ECVAM, is selected as a Marie Curie Training Site for biomaterials testing using radiotracers. In the area of optical imaging, an endoscopic fluorescence based method for tissue characterization was developed, for which a US patent is pending.

The IHCP in Figures–2003

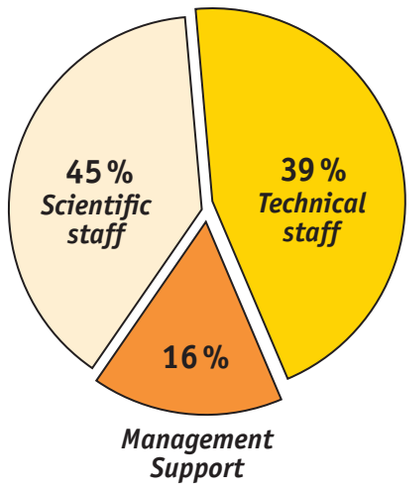
HUMAN RESOURCES

This section gives an overview of the staff situation in 2003 and a historic overview of the staff situation over the last five years, distinguished into statutory and collaborative staff (trainees, PhD and Post Doc grant holders, visiting scientists, national experts).

Statutory staff distribution – 2003

Out of the total JRC staff, IHCP employs 203 statutory staff (including officials, temporary agents and auxiliary agents), and without auxiliary agents a total of 141 staff members:

IHCP Statutory staff
(without auxiliary agents) – 2003



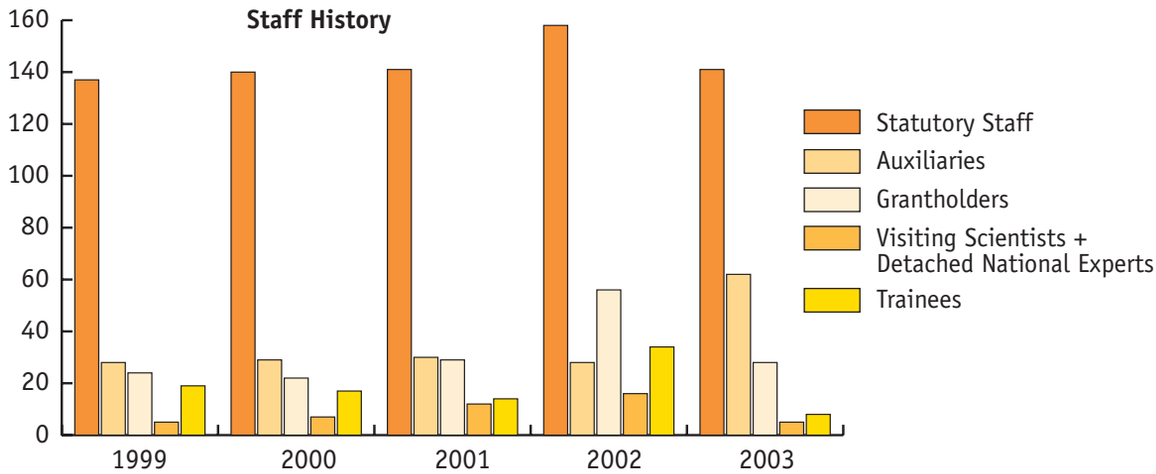
IHCP Statutory Staff (December 2003)	M	F	Total
Officials	60	35	95
Temporary Agents on 5-year renewable contracts	26	19	45
Temporary Agents on 3-year non-renewable contracts	1	0	1
Total IHCP (without auxiliary agents)	**87**	**54**	**141**
Auxiliary Agents on 1-year non-renewable contracts	26	36	62
Total IHCP (with auxiliary agents)	**113**	**90**	**203**

The IHCP statutory staff (without auxiliary agents) consists of 64 (45%) scientific staff, 55 (39%) technical staff, and 22 (16%) staff providing management support. The IHCP scientific staff counts 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.

Collaborative Staff with Member States and Third Countries

The IHCP hosts a large number of collaborative staff (trainees, grant-holders, visiting scientists, seconded national experts) in order to adjust to its research activities. More specifically, the IHCP hosted 41 collaborative staff in 2003:

IHCP Collaborative Staff (December 2003)	M	F	Total
Trainees	5	3	8
Post-Graduate grant-holders	8	11	19
Post-Doc grant-holders	5	4	9
Visiting scientists	3	1	4
Seconded National experts	1	0	1
Total	**22**	**19**	**41**



BUDGET

This section summarizes the financial resources of the IHCP in 2003 and gives a historic overview over the last 5 years. The EU Framework Programmes (FP) for Research and Development set out the general research priorities of the European Union in accordance with Article 169 of the EU Treaty. A total budget of 17.600 M€ was allocated to the Six Framework Programme – FP6 (2003-2007). The JRC (Institutes) received an amount of 1.154 M€ (6.5%) out of the total FP6 budget. The IHCP has been attributed an amount of around 39 M€ for the year 2003.

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

Institutional activities

The JRC defines its broad research areas into its multi-annual JRC Work Programme. The JRC Work Programme is updated annually (annual Work Programmes), and where appropriate, adaptations are made following exchanges with "customer" Directorate Generals to review progress and consider new needs. The 2003 JRC Work Programme is arranged according to the following programme lines: **a)** safety of food and chemicals, **b)** environment, **c)** dependability of Information Systems and Services, and **d)** nuclear safety and safeguards.

The majority of the IHCP projects contribute to the 'Safety of food and chemicals' programme line. The available credits to IHCP are divided into staff expenses, means of execution (maintenance of buildings and equipment, electricity, insurance, consumables, etc.) and operational credits (scientific acquisitions). The following table pre-sents the IHCP institutional budget based on its projects in 2003:

IHCP Institutional Budget 2003–Institutional Projects (K€)

UNIT	ACTIVITIES	Staff costs	Means of execution	Specific credits	Total
ECVAM	Development, validation and promotion of advanced non-animal test methods for chemical substances and products	6,116	170	2512	**8,798**
ECB		8,898	80	788	**9,766**
ECB	Assessment of Chemicals	8,251		675	**8,926**
QSAR's	Development, validation and dissemination of quantitative structure-activity relationships (QSARs)	329		75	**404**
RASEP	Risk assessment in support of EU policies (RASEP): Methodology and refinement	398		38	**436**
BMS		7,129	80	525	**7,734**
Medtech	Medical devices and health technology (MEDTECH)	4,264		325	**4,589**
Nanotech	Nano biotechnologies for health application (Nano Biotech)	2,945		200	**3,145**
PCE		5,816	130	850	**6,796**
Thexas-Chem	Total Human Exposure Assessment Study including toxico-genomic approach (THEXAS-chem)	3,469		325	**3,794**
Thexas-Phys	Total Human Exposure Assessment Study (THEXAS-phys)	1,363		125	**1,488**
BEVABS	European Office for Wine, Alcohol and Spirit Drinks (BEVABS)	1,114		400	**1,514**
GMO	S/T support for the implementation of GMO legislation	4,316	230	1,375	**5,921**
Totals		32,275	690	6,050	39,015

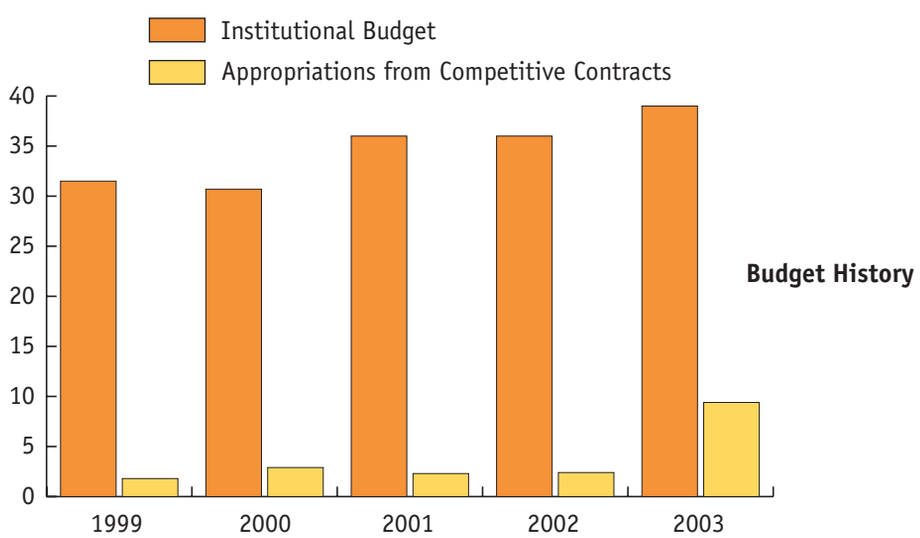
Competitive activities

The advantages of participating in competitive activities are that IHCP gains access to new expertise, and shares its own competencies and facilities. Competitive activities also provide another source of income besides the institutional budget. In accordance with the JRC's own regulations, competitive projects must complement the JRC's mission and must respect the subsidiarity principle.

There are three types of competitive activities:

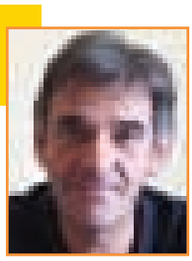
- Participation in shared-cost activities (SCA) with other successful consortia
- Activities financed in the context of other EU policies (non-research) upon request of other Commission services (OCA)
- Work undertaken for third parties on a contractual basis (TPW)

Income from Competitive Activities - 2003 (K€)		
Type	**K€**	**%**
Shared Cost Actions (SCA)	472.894	5
Other Competitive Activities (OCA)	6.523.843	70
Third Party Work (TPW)	2.382.082	25
Total	**9.378.819**	**100**



IHCP Organisational Chart

Director
K. van Leeuwen

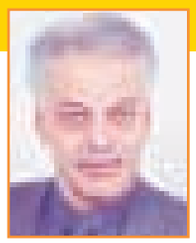


Management
Support[1]
R. Crandon

Biotechnology
and GMOs[2]
G. Van den Eede

European Centre
for the Validation of
Alternative Methods
T. Hartung

European
Chemicals
Bureau
G. Vollmer



Physical and
Chemical Exposure
D. Kotzias

Biomedical
Materials and
Systems
H. Stamm

1. B. De Bernardi served as Unit Head of the Management Support Unit (MSU) until 31st October 2003. Following his retirement, R. Crandon was appointed as Head of Unit of the MSU on 1st January 2004.
2. The Biotechnology and Genetically Modified Organisms (B&GMO) Unit was officially established in November 2002 located in Ispra. G. Van den Eede was appointed as the first Head of Unit on 1st April 2003.

Web information resources
http://biotech.jrc.it/
http://engl.jrc.it
http://gmoinfo.jrc.it
http://gmotraining.jrc.it
http://ihcp.jrc.cec.eu.int

Institutional Project
Support to the Implementation
of the Community Policy on biotechnology and GMOs

Some Shared Cost Actions
GM-FOOD & FEED

Biotechnology and GMOs (B&GMOs)

The IHCP Biotechnology and GMOs Unit (B&GMOs) was created on November 1st 2002. The foundation of this Unit reflects the importance of biotechnology and GMOs for the EU policy and the large amount of requests for technical support made to the JRC. The work of the Unit focuses on the development and validation of appropriate methods for detection, identification and quantification of GMOs in different types of matrices. The Unit operates the European Network of GMO Laboratories (ENGL), which is seen worldwide as a network of scientific reference. The Unit has expertise in environmental risk assessment, in bioinformatics and in issues related to sampling. The Unit works closely with the JRC Institute for Reference Materials and Measurements (IRMM), which is responsible for the production of GMO Certified Reference Materials, and with the JRC Institute for Prospective Technological Studies (IPTS) on the elaboration of topical forward studies.

The IHCP - Biotechnology and GMOs Unit is the JRC reference for the provision of scientific and technical support to the EC biotechnology regulatory framework and for the development of biotechnology expertises in areas relevant to health and consumer protection. The Unit work focuses on the development and validation of appropriate methods for sampling, detection, identification and quantification of Genetically Modified Organisms (GMOs) in different types of matrices. In the context of Regulation (EC) 1829/2003 on genetically modified food and feed, the Joint Research Centre (JRC) of the European Commission and — in particular — the IHCP Biotechnology and GMOs Unit, was appointed as the "Community Reference Laboratory" (CRL). The core task of the CRL is the technical evaluation and validation of detection methods for GM food and feed as fundamental part of the Commission authorisation procedure for GMOs.

The CRL is assisted in this important task by the European Network of GMO Laboratories (ENGL), coordinated and chaired by the Unit itself, and considered as one of the major achievements of the JRC in recent years. The ENGL constitutes a unique platform for experts from EU Member States to discuss technical issues related to sampling, detection, identification and quantification of GMOs.

In support of the Commission policy, the Unit provides specific technical advice and expertise to various Commission Services, such as: the reception of all summary notifications of deliberate field trials (SNIFs), notified under Directive 2001/18/EC, the participation as nominated expert in the development of an operational Biosafety Clearing House and the support to the EU services in the WTO dispute launched by the USA, Canada and Argentina.

The Unit, also in support to ENGL, is actively involved in research projects in the fields of molecular biology, method development and sampling for GMO detection and quantitation. A great deal of attention is also given to bioinformatics, to the maintenance and updating of a database of analytical methods for DNA and protein detection and quantification, and to the development of a molecular register containing DNA sequences of all authorised GMOs.

Over the years, the Unit has developed an *ad hoc* knowledge of the different aspects related to GMO analysis and it has devoted significant effort in transferring this expertise to control laboratories within and beyond actual EU borders. Excellent contacts and collaboration have been established and are continuously strengthened with international research organisations, standardisation bodies (i.e. CEN), as well as with the biotechnology industry.

Further information on the work and activities of the ENGL, including guidance documents and associated information, can be found at: **http://engl.jrc.it**

THE EUROPEAN NETWORK OF GMO LABORATORIES (ENGL)

The European Network of GMO Laboratories (ENGL) is set up to contribute more effectively to the European harmonisation and standardisation of means and methods for sampling, detection, identification and quantification of Genetically Modified Organisms or derived products in a wide variety of matrices, covering seed, grains, food, feed and environmental samples. As such, it is aimed to act as a scientific and technical European Union network of excellence within the context of EU GMO regulation. Projects of excellence and innovation and rapid exchange of data within its members is key to ENGL.

The scope is to create a unique platform for experts that are involved in the sampling, detection, identification and quantification of GMOs — being in the environment, food, feed and seeds — and where technical items can be put forward and discussed, namely:

- Method development for qualitative and quantitative analysis;
- Molecular biology technology transfer;
- Validation and proficiency studies of methods suitable either for screening of various matrices for the presence of GMOs, or for the estimation of the GMO quantities present;
- Reference material (the responsibility for this work package lies with the JRC's Institute for Reference Materials and Measurements);

- Sampling strategies and procedures for different GM-commodities (seeds, grains, raw material, products for final consumer or mass caterers);
- Databases and bioinformatics and requirements for unique identification of GMOs and setting up of databases that contain these molecular data;
- Training has been organized at the Ispra site.

Members of this Network, inaugurated in Brussels in December 2002 in the presence of Research Commissioner Ph. Busquin and of the Director General of the JRC, Mr B. Mc Sweeney, met in 2003 several times for plenary sessions, for steering committee meetings and *ad hoc* working group meetings addressing specific relevant topics. The 2nd official plenary session has been held in April and the 3rd plenary session in November.

ENGL invited EU member states and future AC member states to all the working group sessions and its role is also to support and facilitate the interaction with all global trade partners. During all plenary meeting a number of experts from Accession Countries were invited to be present as observer. In 2004 ten New Member States will join the Network as official members nominated by Competent Authorities of their own countries. By mid-2004, over 70 laboratories will have an official membership to ENGL.

VALIDATION OF METHODS FOR GMO DETECTION

Method validation for GM detection is an area where the JRC is actively involved and this commitment has grown considerably since 2002. In particular, the Regulation (EC) 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed establishes the Community Reference Laboratory (CRL) and the Annex of the Regulation lays down the duties and tasks of the CRL. The CRL is the Joint Research Centre, assisted by the ENGL in its main task: the validation of methods with respect to the GM Food and Feed Regulation. The Regulation entered into force on April 18th, 2004.

For its preparation, the Unit led in 2003 an ENGL Working Group on Validation. As a result, a document "Definition of minimum performance requirements for analytical methods of GMO testing" was accepted by the ENGL Plenary Meeting in November 2003. The document provides information about the criteria and requirements for method validation with respect to the regulatory compliance and control purposes. The document was also used as a guideline during the drafting of the Regulation (EC) 641/2004 in which CRL procedures are defined and described.

In 2003, method validation was mainly carried out within the EU shared cost action project QPCRGMOFOOD. Altogether, about 25 multi-laboratory validations with at least three laboratories have been carried out within the project. Among those, methods satisfying pre-validation requirements were then selected for a full ring-trial with more than 10 participating laboratories (i.e. extraction methods for maize matrices as well as Zein, ADH, HMG and Invertase reference gene systems for maize) — and some of them were later validated in the context of regulatory compliance (event-specific quantitative PCR methods for Bt11 and T25 maize lines). The project has contributed also to the development, testing and implementation of the modular validation approach, in which the extraction methods, reference gene systems and GMO-specific systems can in principle be validated separately. Concurrently, the approach has been adopted by the CEN and is suggested to form the frame for the standardization of GMO testing methods within Europe. In 2003, the Unit in collaboration with the ENGL concluded the first validation process directly related to a GM authorization in Europe — for the approval for marketing of sweet maize derived from maize Bt11. The results were presented to the EC Standing Committee in November 2003. Concurrently, several validation studies related to the GM authorizations were launched in anticipation of the CRL establishment (e.g. for the detection of NK603 and GA21 maize).

In the context of FP5 (Fifth Research Framework Programme), the Unit participated in a number of research projects, which have been completed successfully (such as ENTRANSFOOD and QPCRGMOFOOD). A number of new methods have been developed and validated. The Unit was also involved in the preparation of new research project proposals: SIGMEA (Sustainable Introduction of GMOs into European Agriculture) and Co-extra (GM and non-GM supply chains: their co-existence and traceability). Both proposals were successful: SIGMEA project officially started in May 2004, and the Co-extra proposal is at the contract negotiation stage. In both projects, the Unit is in charge of coordinating a work-package related to GM detection and sampling. Several members of the ENGL also participate in these projects.

Activity of Proficiency Testing (PT)

Proficiency Testing (PT) is a quality tool that measures the outputs of a laboratory. The Unit is actively involved in PT, which is a requirement for the implementation of analytical quality systems. The PT schemes to which the molecular biology laboratory has participated are:

- GeMMa (Central Science Lab. – York, UK) Food Analysis Performance Assessment Scheme - 9 Rounds
- USDA – Gipsa (Grain Inspection Packers and Stockyards Administration) – 3 Rounds

Several types of samples have been analysed during PT activity, including meat pâté, soya milk powder, sausage meat, animal feed, cakes and biscuits. Analyses have been carried out for GMO screening, identification (qualitative methods) and quantitation. A number of analytical techniques have been employed, including PCR, nested PCR, real-time PCR and immunoassay tests (Lateral Strip Test). Particular focus has been put on identification and quantitative analysis of mixtures of GM maize events present in the same sample. The laboratory sensibly extended its capacity to reliably analyse an increasing number of GM events: routine analyses on GM maize lines GA21, MON863, NK603, MON810, Starlink, Bt176, T25 and Bt11 are now carried out. Excellent scores for the results produced have constantly been received.

Collaboration with IRMM for the certification of CRMs

In the context of new methods validation, candidate Certified Reference Materials of maize GA21 and MON863 were provided to the Unit by JRC-IRMM for pre-marketing testing. Sample were extracted and tested on real-time PCR, specifically for intra and inter-bottle homogeneity, an important parameter assessed before commercialisation of CRMs. Results were provided to the IRMM as supporting data for the certification of these materials.

SAMPLING

During 2003 the Unit continued its activity for the identification and development of appropriate sampling strategies to support EU legislation for the detection and quantification of GMOs in different market products. Progresses were achieved in the four components structuring the sampling research area: theoretical-statistical work, software development, KeLDA research project, and ad-hoc technical advice.

Theoretical-statistical work

Following the publication of a new approach to investigate the effects of different levels of heterogeneity on the accuracy of different sampling plans for the detection of GM particles within kernel lots, we have developed a novel statistical model to assess incremental sampling efficiency as function of lot heterogeneity. In particular, the model allows estimating the sampling error associated to different sampling protocols (in terms of both number and size of samples taken from the lot), applicable to any consignment of particulate material with respect to any kind of contamination, including GMOs. The novelty of our approach is the freedom from any distribution constraints. This new model is at the basis of the sampling protocols for grains recommended in the EU Recommendation "on technical guidance for sampling and detection of GMOs and material produced from GMOs as or in products" in the context of Regulation (EC) 1830/2003.

Software Development

KeSTE (Kernel Sampling Technique Evaluation), a software designed to evaluate suitability of sampling strategies to detect impurities of large kernel lots virtually created (investigative tool) or actually sampled (data analysis supportive tool), was distributed at the second ENGL plenary meeting (April 2003). KeSTE is now available on the web, free-of-charge.

KeSTE software

During 2003 the B&GMO Unit started to develop a new software *CoDE* (Contaminant Distribution Estimate) designed to quantify the sampling error associated to different sampling protocols according to the Unit's new distribution-free statistical model. *CoDE* will be distributed during 2004. It will serve as a supporting tool for the implementation of the sampling protocol defined in the EU Recommendation in the context of Regulation (EC) 1830/2003.

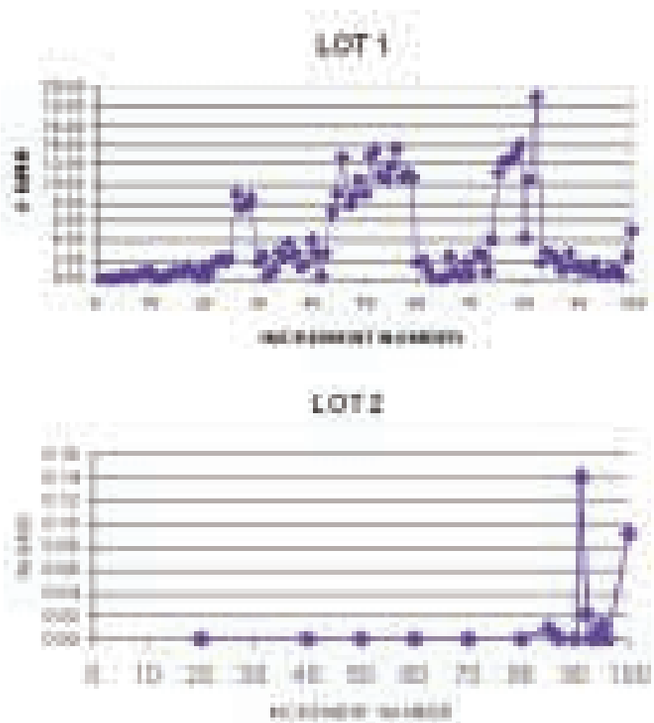
CoDE software

EU pan-project KeLDA

KeLDA (Kernel Lot Distribution Assessment), initiated in December 2002, is the first research project investigating the degree of heterogeneity present in real lots and providing real data on this issue, worldwide. During 2003 participant laboratories from 10 Member States have sampled and screened 12 soybean lots (100 samples per

lot, which had been homogenized and grinded by JRC-IRMM), for the presence of GM materials. The B&GMOs Unit is responsible for the quantitation of all positive samples and has completed the analysis of five lots during 2003. The obtained preliminary results indicate that GMOs distribution can vary among lots (see figure below) and it cannot be assumed *a priori* to be random, as currently done by most internationally adopted sampling protocols.

KeLDA project: off-loading of a lot



KeLDA lots: distribution patterns of GM contaminations

Technical advice

In order to support the achievement of sampling harmonization, the B&GMO Unit has provided technical advice both internally to DG SANCO and DG ENV for the definition of sampling protocols in the context of the new EU GMO-related legislation, and externally to CEN for the definition of a new CEN-ISO Sampling Standard (prEN ISO 21568:2003).

MOLECULAR BIOLOGY LABORATORY

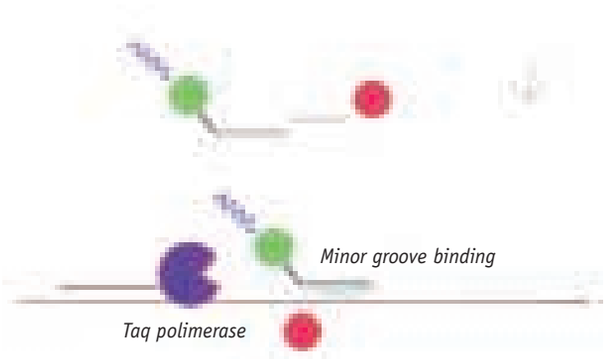
The need to comply with mandatory threshold and labelling requirements introduced by the new GM food and feed (1829/2003) and traceability (1830/2003) Regulations has increased the need for new and reliable methods for GMO detection in food and feedstuffs. The B&GMO Unit is the JRC reference for the provision of scientific and technical support to the EC biotechnology regulatory framework and to develop biotechnology expertise in relevant areas for health and consumer protection. It has dedicated considerable efforts to the development, optimisation and validation of molecular biology-based methods.

Methods development and optimisation

The research activity of the Unit focused on the following projects:

- Development and optimisation of a multiplex real-time PCR based system for the quantification of the CaMV 35S promoter in GM maize lines. The project started in the year 2002 and was completed during the first half of 2003. The method, developed and optimized on maize MON810 for a reliable estimation of the GM content, has been applied for the study of the effect of target copy number in different GM events on the accuracy of GMO quantitation. The method is currently used in GMO quantitation in the frame of activities of Proficiency Testing carried out by the B&GMO Unit. Following an expression of interest for this method at European level, the organization of a collaborative trial for its validation during 2004 is foreseen.

- Development and optimization of real-time PCR systems using novel probe systems (MGB – minor groove binding). The aim of the project was to assess and compare the efficiency of the novel probe design with respect to the traditional Taqman degradation probes. A multiplex method for the quantitation of the Roundup Ready soybean was developed and characterized. The performance criteria, studied during the in-house validation of the method, showed that this system could be successfully applied to the quantitation of GM soybean in raw materials. Moreover, due to the characteristics of stability and sensitivity offered by the innovative real-time chemistry, the method allows for improved quantitation of GM ingredients in highly processed materials.



Minor Groove Binding (MGB) probes provide higher specificity and stability in GMO quantitative analysis

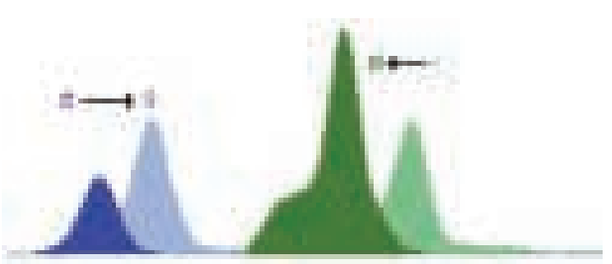
- Reference genes copy number in maize (the pTetra Project). The relative quantification of a GMO with the real-time PCR technique is achieved by normalising the number of genetically modified genomes with the number of total genomes of the given species, determining the amount of a GMO specific sequence and of a species-specific endogenous reference gene. The variability in the copy number of the most used reference genes causes major problems in the accurate quantitation of GMOs, leading to significant analytical errors. With the aim to address this problem and develop a novel approach that could help improving the precision of the tests, a plasmid containing the target sequences of four maize reference genes (Zein, Invertase, HMG and ADH) was constructed; the reference genes were inserted in a 1:1:1:1 ratio. The plasmid was used as an equimolarity-based reference material allowing the direct quantification of the four reference genes in maize. The studies, conducted on 30 different GM and wild type maize lines, demonstrated that different endogenous genes present a certain degree of variability across the species, and this variability has a negative impact on the accuracy of GMO quantitation. The most stable endogenous gene was identified and its use in GMO testing implemented and recommended.

- Plasmid-based reference materials for the quantification of GMOs. Plasmids are a promising alternative to the matrix matched certified reference materials commonly used in GMO detection, due to their ease of production, low cost and flexible possibility of use. The project led to the production of tandem-marker plasmids containing simultaneously specific target sequences for the GMO of interest and a species-specific reference marker sequence in a 1:1 ratio. These plasmids have been tested and calibrated as real-time PCR standards for the use in GMO quantitation. As well as serving as reliable standard materials, the plasmids developed represent a powerful molecular tool in determining the precise relative dosages of the transgenic sequences with respect to endogenous species-specific markers in transgenic maize lines.

Genomics

According to Regulation (EC) 1829/2003 on Genetically Modified Food and Feed, an application for authorization of GM food needs to be accompanied by a method of detection and identification of the transformation event. Detection methods for GM constructs are mostly based on GM specific DNA sequences and, often, also on plant specific DNA sequences that flank the inserted transgene (event specific detection method). These detection methods rely on the assumption that the GM inserts remain stable in the genome. However, little is known about the fate of a GM construct, once it is introduced in the plant genome. What is the effect of conventional agricultural breeding or what might be the influence of environmental conditions and stresses on the integrity and the position of the insert, the flanking plant regions?

Stability of transgenic constructs is being studied in our Unit, in an ongoing collaboration with the CLO in Belgium. Part of the project consists of a detailed characterization of several GM constructs, integrated in the plant. Another part involves a study of the stability of the TDNA transgene in several lines of the model plant *Arabidopsis thaliana*. Since several thousands of plants will be screened, a significant effort was invested in the year 2003 in developing analysis techniques that are fast, reliable and repeatable: quick plant DNA extractions and a semi high-throughput analysis system, using fluorescent labelling of the DNA fragments combined with an analysis via capillary gel-electrophoresis. The technique of Single Site Conformational Patterns (SSCP) was established with a variety of plant-derived DNA fragments. This allowed the detection of rearrangements that affect the conformation of a DNA fragment: single nucleotide differences (SNP: single nucleotide polymorphisms), deletions and insertions.



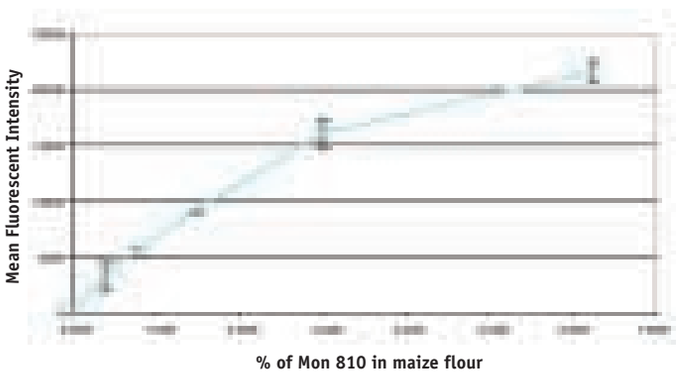
Single Site Conformational Pattern of 2 DNA fragments with 1 nucleotide change: C to G.

Proteomics

During 2003, a new approach for the detection and quantification of GMO specific proteins in raw materials, based on Luminex technology, was developed. The methodology allows the quantitation of MON810 and Bt11 specific proteins in maize flour samples. The assay has been proven to be applicable over a broad range of GM contamination levels (0.1% to 100%).

In addition, the optimization of a multiplex protein assay was initiated in 2003 and it is on going. In order to overcome the lack of commercially available antibodies, a specific set of selected proteins (CRY1AB and EPSPS) were successfully expressed *in vitro*. These proteins were used as calibrants for the system and will be used for the production of the corresponding antibodies.

Although protein-based methods are not at present widely applied in Europe, they can find practical applications as cost and time efficient tools for GMO screening and for multi-events analyses. In order to verify if ELISA-based methods can be a valuable alternative to DNA-based methods for GMO surveys, our Unit is comparing the performance of some of the most commonly used ELISA kits.



Quantification of MON810 and Bt11 GMO proteins in maize flour samples using Luminex MAP technology.

Training

The activity started in the year 2000 as part of the collaboration between JRC and WHO to promote food safety related issues in WHO European Region, inside and beyond current EU borders, with special consideration for Accession Countries, as well as Central and Eastern Countries with transitional economies. The experience was very positive followed by intense contacts with the participants, who frequently requested our advice for the implementation and/or optimisation of laboratories devoted to the analyses for GMO detection. A second series of three Training Courses was organized in the years 2002-2003, with extensive participation of candidates from Accession Countries.

To enlarge and enhance the benefits of training and to support local training initiatives, the B&GMO Unit explored the possibility to act as a Training Centre for trainees. For this purpose, one scientist from the Agricultural Biotechnology Centre (Environmental Biosafety Research Institute - Gödöllõ, Hungary) was hosted for 2 months in the B&GMO facilities. As a successful follow up of this initiative a Training Course, specifically directed to Accession Counties, took place in Gödöllõ, in November 2003.

Training Course in Gödöllõ

Additionally, a training manual as a permanent source of information describing all the techniques currently used for the detection and quantification of GMOs was produced, edited and published in 2003 (**http://gmotraining.jrc.it/**). The manual covers a wide variety of techniques for GMO detection, identification, characterisation, and quantification, including theoretical information crucial for anyone wishing to enter the field of GMO detection. The manual, which is the first one published on this topic, is currently being translated into Turkish and Russian for further publication.

E-training tools within the JRC Enlargement action

In order to reinforce the Enlargement Action and respond to the continuously increasing need of training beyond the available training capacity, a new strategy based on the use of multimedia tools for training was proposed and introduced. The aim is to increase efficiency, productivity and availability of training efforts by complementing traditional training courses with new tools, such as interactive DVD training. Among other topics, GMO was selected as the topic for the first pilot e-training project to be developed. During 2003 large effort was devoted to the production of this multimedia interactive didactical product. Theoretical lessons and seminars (as slide shows with verbal explanation), illustrations of practical laboratory work (videos explaining each step of the procedures), and relevant documents (manual, glossary and web links) will provide all information needed for the

analysis of GMOs, in multimedia interactive format resembling a traditional training course. This activity is still ongoing and the release is expected in 2004.

Finally, during 2003 three DNE/VS from Romania, Czech Republic, and Poland were hosted and trained for a total period of 10 months. During this period, specific individual work programmes were followed to respond to individual specific needs in the field of GMO detection, and to allow direct participation in ongoing research activities.

BIOINFORMATICS AND ANALYTICAL METHODS DATABASES

During 2003, efforts on building a bioinformatics expertise were focused mainly on pursuing the development of the ENGL Molecular Register and the GMOs methods database. In response to the request of the allergen expert community addition the Unit has assessed the current state of the art of publicly available allergen databases and associated bioinformatic tools.

ENGL Molecular Register

The Unit, with the input of competent authorities, bioinformatics experts and computer scientists, compiled the ENGL Molecular Register. This Register provides access to a GMO events database and to relevant analysis tools. The Molecular Register contains all available sequencing information and reference material for GMOs authorised to circulate within the Community. It also contains, where available, relevant information concerning GMOs that are not authorised in the European Union. The development of the Molecular Register is now completed and the prototype is currently being tested before final release.

Reference Allergen Register

One of the main conclusions of an ad hoc meeting on Allergen Database was the need to identify the current state of the art of publicly available databases and associated bioinformatics tools.

As a complement to the activity on the Reference Allergen Register itself, the Unit is participating to the INFORMALL concerted action project. The 3 years project, which started in 2003, aims at developing communication strategies in the food allergy area and promoting the provision of visible, credible sources of information appropriate for different stakeholders including consumers, industry and regulators.

GMO methods database

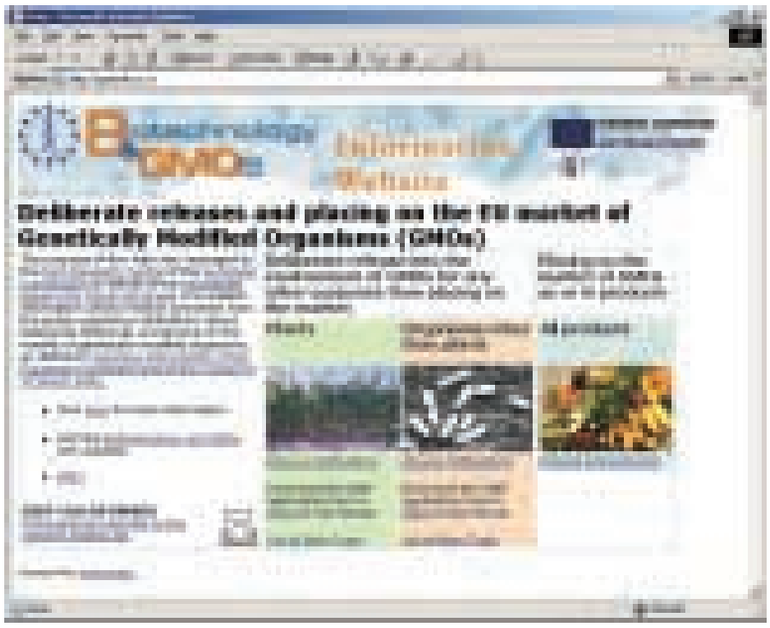
The new Regulation (EC) 1830/2003 on traceability and labelling requires the adoption of appropriate and cost-effective control and inspection measures for the analysis of GMOs in the food chain. Access to reliable information on methods for the detection, identification, and quantification of GMOs is then fundamental for legislative enforcement. The Unit developed a database (**http://biotech.jrc.it/**) to allow direct and user-friendly access to information regarding methods for GMO analysis. The database is organized in three sections: **1)** general information on the GMO and the corresponding method; **2)** technical information on the method; **3)** specific information on the proficiency of the method and its validation status, if available. During 2003, the structure, data content and layout of all three sections were improved: in order to facilitate the selection of the appropriate method, 105 new fields have been included. In December 2003, upon the request of DG SANCO, the GMO database was also updated with data from the CODEX Alimentarius database, which includes methods reported by member countries. The database contains now 390 records and more than 600 visitors consulted it during the last three months. This resource is highly appreciated by a wide range of users at the international level and by Commission Services. Indeed it will be included, as a reference link for provision of information on methods of GMO analysis, in the Commission Recommendation on technical guidance for sampling and detection of GMOs, in support to the Regulation (EC) 1830/2003.

DATABASES AND INFORMATION TO THE GENERAL PUBLIC

GMO Notifications Summary (SNIF)

Since many years, DG Environment and Member States' Competent Authorities (CA) have mandated the JRC to provide electronic means for the exchange of information on the Summary Notification Information Format (SNIF), according to Directive 2001/18/EC which collects all data related to EU deliberate field trials involving GMOs. An Intranet-based system, called WebSNIF, has been developed to allow CAs and the European Commission to circulate the appropriate amount of information by granting the necessary level of access and security to each user.

A second function of the system is to provide access to an open Internet site **http://gmoinfo.jrc.it/** from where, as required by Directive 2001/18/EC, information on products approved for products approved for marketing is published and where the general public can submit comments. During 2003, the system allowed the circulation of 82 SNIFs regarding deliberate field trials, and 23 SNIFs regarding placing on the market. The statistics of the website reveal that the interest in the subject is not only limited to the European Union, as an important percentage of the visits came from outside EU. Visits originate from both the general public and professional/scientific sources.



B&GMOs webpage

INFORMATION SYSTEMS IN SUPPORT OF THE REGULATORY PROCESSES

DG ENV has requested the exchange of information between Member States, the European Commission and the general public in the framework of Directive 2001/18/EC regarding:

- Reception, management and on-line publication of summary notification information describing small scale field trials;
- Reception, management and on-line publication of all part C notification dossiers, plus timely handling of public comments, comments from Member States, requests for additional information, etc.

The support given by the B&GMO Unit has served as an example for the Biosafety Clearing House under the Cartagena Protocol and link with other OECD initiatives. The existence of a single biosafety platform serving the needs of different pieces of legislation is going to facilitate Member States in fulfilling the provision of information required by the different legislative tools. Financial assistance was requested from IDA* to support the development of a tracking system, inclusive of a document management system and a GMO register (GMOREGEX).

GMOREGEX

The purpose of the GMOREGEX project is to implement an automated system in support of all activities related to the exchange of information between Member States Competent Authorities, the European Commission and the general public, as defined in Directive 2001/18/EC. The system will include a register for the purpose of recording the information on genetic modifications in GMOs, as specified in the Directive. The system will make use of IDA generic services that have been implemented for fostering information systems interoperability through the creation of a coherent framework, consistent quality assurance standards and best practices. These services include a pan-European IP network, similar to the Internet, dedicated to inter-administrative requirements (TESTA), a communication and information administration system (CIRCA) supporting the cooperative activity of committees and working groups, and a PKI (Public Key Infrastructure) facilitating secure communications and the use of electronic signatures.

The project started at the end of January 2003. The preparatory phase is now completed, during which a thorough analysis of Directive 2001/18/EC to define the business process involved in the timed exchange of information. A system prototype was developed for testing the most appropriate technologies. The next steps will be the analysis of the documentation format and/or structure, including a preliminary definition of how the

* IDA = Interchange of Data between Administrations: IDA is a European Commission driven strategic initiative using advances in information and communications technology to support rapid electronic exchange of information between Member State administrations. The objective is to improve Community decision-making, to facilitate operation of the internal market and to accelerate policy implementation.

notification dossier should be structured, using syntax such as XML, in order to ensure efficient handling.

Biosafety Clearing House

The JRC has been nominated as the Biosafety Clearing House (BCH) Focal Point (FP) for the European Community. The secretariat of the Convention on Biological Diversity (the Biosafety Clearing House — BCH) has requested the expertise of the B&GMOs Unit to support the increase of inter-operability between the BCH and the information flow in the EU. Tasks of the EU BCH FP a national/regional FP include: **1)** liaising with the CBD Secretariat regarding technical aspects of national participation in the Biosafety Clearing-House; **2)** validating records at a national/regional level, making them publicly available through the central portal, and facilitating the development of an interdisciplinary network; **3)** coordinating the distribution of information with Member States FP, which are also parties to the Cartagena Protocol and have been nominated a National BCH Focal Point.

The Unit already started the activities in the information submission and dissemination and it is currently organizing the coordination with the MS focal points. Activities for the next months include the design and development of a web-based application, conforming with the technical requirements of the CBD BCH portal and interoperable with both the CBD BCH portal and the National BCH FP of the Member States.

RISK PERCEPTION: SCIENCE, PUBLIC DEBATE AND POLICY MAKING, 4-5 December 2003

Understanding the process(es) of risk perception, and finding ways to take account of it in policy making so as to increase the public's trust in science based regulation, has become a political imperative in modern governance. Nowhere is this more apparent than in the area of GM agri-food. This major international conference, organised on behalf of DG-SANCO, under the Commission's Life Science and Biotechnology — A strategy for Europe initiative, and hosted by the European Commission in Brussels, brought together leading international experts, key opinion formers, and decision makers to debate issues surrounding risk, the perception of risk, and its interplay with the citizen, society and governance. Under the auspices of Mr David Byrne, European Commissioner for Health and Consumer Protection, a wide selection of world experts and international opinion formers addressed some of the finer elements of human behavioural psychology, such as human behaviour based on perception, rather than fact, as well as broader sociological considerations such as societal values in the interpretation of risks and perceived risks, against the wider dimensions of varying cultural influences, particularly in relation to GM issues including the need for improved management strategies of risks and perceived risks. Over 530 delegates participated over two days. Copies of the speeches and presentations can be found on the DG-SANCO website at **http://europa.eu.int/comm/food/risk_perception/index.htm**

CONCERTED ACTION: ENTRANSFOOD (European Network Safety Assessment of Genetically Modified Food Crops)

In 2000, under FP5, the thematic network European network safety assessment of genetically modified food crops (ENTRANSFOOD) was launched with the specific aim of identifying research strategies and tools to address issues related to safety and management of transgenic food products, and in particular the relationship to testing or assessment of food containing or produced from GMOs. The Unit was responsible for the co-ordination of the working group concerning gene transfer in relation to the safety of food and feed derived from GM-plants. This working group was further linked to the previous GMOBILITY project and concluded in May 2003.

SHARED COST ACTION: QPCRGMOFOOD (Reliable, standardized, specific, quantitative detection of genetically modified food)

In 2002 the unit played a central role in the shared cost action QPCRGMODOOD project, also under FP5, which aimed at developing reliable and transformation-event-

specific tests for qualitative and quantitative detection of genetic modifications in food, including event-specific multiplex tests for determination of the diversity of genetic modifications in food, and how the implementation of such methods would impact on the overall consumer confidence in food security and trust in science and risk regulators. The unit was charged with the co-ordination of a work package dedicated to the validation of all methods developed in the other work package, in particular extraction, event-specific detection and event-specific quantitation. This approach included responsibility for the designs of the ring-trials, study organisation, data analysis, evaluation and eventual method recommendation for application. The work involved the development of a general scheme for validation studies, and in the second half of 2002, reference gene systems for maize, soybean and oilseed rape as well as DNA extraction methods for different maize and soy matrices were tested in multi-laboratory validations. In addition, the pre-validation of nine quantitative GMO-specific methods was launched. This project concluded in 2002.

B&GMOs SELECTED PUBLICATIONS IN 2003

BRUSIC, V., N. PETROVSKY, S.M. GENDEL, M. MILLOT, O. GIGONZAC, S.J. STELMAN. 2003. "Computational Tools for the Study of Allergens". *Allergy,* 58: 1083-1092.

BRUSIC, V., M. MILLOT, N. PETROVSKY, S.M. GENDEL, O. GIGONZAC, S.J. STELMAN. 2003. "Allergen Databases". *Allergy,* 58: 1093-1100.

PAOLETTI, C. 2004. GMO "Analysis: Sampling, the European Perspective". In: *Testing of Genetically Modified Organisms in food*. Editor: F. Ahmed, East Carolina University School of Medicine. The Haworth Press Inc., NY-USA.

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QUERCI M., JERMINI M., AND VAN DEN EEDE G. eds. 2003. *The analysis of food samples for the presence of Genetically Modified Organisms. User Manual.* European Commission - Joint Research Centre. Special Publication No. I.03.114. 206 pages.

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http://ecvam-sis.jrc.it/
http://ihcp.jrc.cec.eu.int

Institutional Project
The validation of alternative methods

European Centre for the Validation of Alternative Methods (ECVAM)

The European Centre for the Validation of Alternative Methods (ECVAM) is an international reference centre for the development and validation of alternative testing methods to replace, reduce or refine the use of laboratory animals in the biomedical sciences with emphasis on toxicological assessments.

ECVAM was established by a communication of the European Commission (SEC 91/1794) referring to a requirement in the animal protection Directive 86/609/EEC.

ECVAM's work is focused on the development and evaluation of *in vitro* methods (e.g. cell and tissue cultures), the use of computer modelling based on structure-activity relationships, and on physiological and biokinetic modelling.

ECVAM's role is to co-ordinate international validation studies, to act as a focal point for the exchange of information, to set up and maintain a database on alternative methods, and to promote dialogue among legislators. Moreover, ECVAM plays an active role in the pre-normative research activities of the JRC.

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

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

ECVAM AND THE CHALLENGE OF EUROPEAN POLICIES

The new EU Chemicals Policy will require the assessment of some 30,000 chemicals, which will have serious financial and animal welfare implications, unless alternative methods are developed and validated, and eventually implemented in the context of the REACH system. The 7th amendment of the cosmetics directive (Council Directive 2003/15/EC) foresees phasing out animal experiments within 10 years. Consequently, the overall aim of ECVAM is to provide support to the future Chemicals Policy and Cosmetics Directive through the development, validation and promotion of non-animal methods, especially those designed for the testing of chemical substances and products (including cosmetics, medicines and biologicals) and biomaterials, and the operation of specialised databases.

In the light of the recently emerged new expectations from both the European cosmetics directive and the chemicals policy, ECVAM has restructured its services by directly targeting the animal tests to be replaced. 11 key-areas have been established or were reinforced with the support of various working groups with participation of stakeholders and international experts (for details see the ECVAM website: **http://ecvam.jrc.it**).

Moreover, in support to the implementation to the 7th amendment of the cosmetics directive, ECVAM co-ordinated the creation and operation of ad-hoc international working groups to access the state-of-the-art of alternative methods for human health effects, in support to a jointly established working group of Commission services and stakeholders.

ECVAM'S MAIN ACHIEVEMENTS

The following list summarises the most important achievements since its foundation in 1991.

Validation of alternative methods to animal experimentation

8 alternative testing methods have been endorsed by the ECVAM Scientific Advisory Committee as scientifically valid for skin corrosivity, phototoxicity, embryotoxicty testing, as well as for percutaneous absorption of chemicals. Furthermore, *7 alternative methods* reached scientific acceptance for mainly potency testing and safety evaluation of biologicals, such as vaccines, as well as for the production of monoclonal antibodies. A further four cell-based tests successfully passed the multi-partner validation project on monitoring side effects, such as fever reactions, arising from contaminants of injectable drugs which could save the lives of about 200,000 laboratory rabbits per year in Europe.

The ECVAM validation study to predict adverse effects of anticancer drugs on the blood forming system, causing acute neutropenia, has successfully been completed.

The following methods granted regulatory acceptance by International bodies:

- Reconstituted dermal models (EpiSkin™ and EpiDerm™) and the TER test for skin corrosivity testing and the 3T3 Neutral Red Uptake for phototoxicity testing. All were accepted by both the European Commission (Annex V to Council Directive on dangerous substances 67/548/EEC) and the Test Guideline Programme of the Organisation of Economic Cooperation and Development (OECD). Furthermore, ECVAM

actively supported and/or endorsed alternative refinement tests for skin sensitisation and acute oral toxicity testing. After the regulatory acceptance a 50% reduction of animal use for skin sensitisation and a reduction of animal use by a factor of three compared to previous test guidelines for acute oral toxicity was achieved.

- Three potency tests of biologicals have been accepted by the European Directorate for the Quality of Medicines (European Pharmacopoeia).

Modified from a design by B. Lucaroni, DG RTD

ECVAM as a focal point for information exchange and the promotion of dialogue between all involved parties in the alternatives area including legislators

Since its foundation, 48 ECVAM workshop reports have been published in peer-reviewed journals as an outcome of expert group meetings organised by ECVAM reviewing the state-of-the-art of non-animal test development in various areas. 15 Task Forces were established to focus on more tightly defined targets.

ECVAM organised the 3rd World Congress on Alternatives and Animal Use in Life Sciences, held in Bologna in 1999, with the participation of nearly 800 participants from 39 countries. It comprised in several plenary lectures, 35 parallel sessions, 26 workshops, four point/counterpoint sessions and 250 poster presentations.

In 2002, ECVAM organised a Status Seminar with its collaboration partners and stakeholders to critically review the contributions of ECVAM and to identify priorities for future activities with regard to its four main tasks and with emphasis on the EU Chemicals Policy, the 7th Amendment to Directive 76/768/EEC on Cosmetics and Directive 86/609/EEC on animal welfare.

Establishment of a database on alternative methods

ECVAM has established a Scientific Information Service (SIS), which consists of three projects: databases providing factual and evaluated information on various aspects of animal alternatives at any stage of development and validation, the international *ECVAM Thesaurus* project and the *ECVAM website*. SIS went the first time online in 2001 and has currently 2900 registered and active users from 65 countries.

In addition, numerous supplementary activities have been undertaken to comply with ECVAM's overall mission. Selected key achievements and events are listed hereafter:

- International harmonisation of the principles for scientific validation of alternative methods (ECVAM Workshop Report 5. "Practical Aspects of the Validation of Toxicity Test Procedures". Balls *et al.* (1995) ATLA 23, 129-147).

- International standardisation of laboratory practices in the field of *in vitro* techniques through the establishment of Good Cell Culture Practices (GCCP) along the principles of Good Laboratory Practice (GLP) leading to a guidance document on GLP for in vitro toxicology which were submitted to OECD jointly by ECVAM and the US Interagency Coordination Committee on Alternative Methods (ICCVAM).

- 1st Meeting of the OECD Expert Group on (Q)SARs hosted by the JRC in 2003 to develop a two-year work programme for the newly established OECD activity on (Q)SARs, which was approved by the OECD Joint Meeting the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology in June 2003. The JRC will play a leading role in its implementation.

ECVAM'S ORGANISATION: THE 11 KEYS AREAS

Systemic Toxicity (acute and chronic)

Systemic and repeated dose toxicities represent a big challenge for ECVAM, since in these two fields, only some reduction or refinement methods have been developed, i.e. methods, which reduce the number or the suffering of the animals, but still are animal experiments (e.g. Local Lymph-Node Assay for sensitisation). With regard to animal consumption, the systemic and repeated-dose tests make up a substantial proportion of all animals

used. For the first time complex tiered testing strategies have to be composed and validated. This requires an entirely new toolbox for risk management. This conceptual framework shall be deduced and elaborated in a series of consensus workshops. As a consequence, this will be utilised for the key areas of long-term and systemic toxicities in the future (reproductive toxicity, acute, repeated dose and chronic toxicity as well as carcinogenicity).

A workshop on acute toxicity was held in September 2003 to develop a strategy to replace animal tests in acute toxicity testing. The recommendations are reflected in the Integrated Project Proposal A-Cute-Tox, which was submitted to DG RTD in November 2003, and the contract is now under negotiation.

In the specific areas of *haematotoxicity and immunotoxicity* the activities are focussed on the optimisation and validation of in vitro tests for assessing the cytotoxic effects of chemicals, and on the development of prediction models for extrapolating these effects to predictions of acute lethal toxicity in animals and humans. *In vitro* haematotoxicology provides the opportunity to study the effects of toxicants directly on relevant human target tissues, reducing toxicological uncertainties due to animal/human extrapolation, and giving its knowledge and experience necessary for applying this kind of model to other continuously renewing tissues in the body. Moreover, a genetic damage to haematopoietic cells may occur in the absence of any overt haematological signs. The development of tissue-specific screening systems which are able to give information about toxic effects of chemicals, drugs and environmental hazards on target genes is needed in order to make preliminary decisions or set priorities for selection among large groups of chemicals and possible drugs.

In the area of repeated and chronic toxicity testing *in vitro* activities have been started aiming to identify priorities and to start defining a testing strategy. Two research projects to investigate the damage caused by Ochratoxin A to renal proximal tubules and to evaluate the usefulness of molecules of plant origin to replace animal serum in cell cultures were successfully completed. An FP6 STREP project, PREDICTOMICS, entitled "Short-term in vitro assays for long-term toxicity" has been funded by DG RTD and ECVAM is involved in the Executive board.

In the context of the Cosmetic Directive, estimated timetables for the provision of alternative methods for acute, subchronic and subacute toxicity have been prepared.

Topical Toxicity

New activities in the field of eye irritation were initiated with the scope of achieving the validation of alternative methods to replace the traditional Draize rabbit eye test. They involve:

- The evaluation of the in vivo variability of the Draize Eye Test, based on literature research and on data collection.
- The evaluation of alternative methods aiming to refine the existing animal test, such as the Low-Volume-Eye-Test.
- Data collection and retrospective evaluation of the most promising *in vitro* methods that might partially or completely replace the animal test.

With regard to the ECVAM international validation study on the EpiDerm and EPISKIN assays and the SIFT for the prediction of acute skin irritation, the logistics were organised, contracts were established and test chemicals selection for phase 1 was completed.

An *"ad hoc* Group" between Commission services and stakeholders was set up to establish an objective state of play for the evaluation of the current status of alternative methods/strategies and the prospects for their validation and regulatory acceptance. Additional scientific experts on the 11 human health effects of concern were nominated. ECVAM coordinated the scientific discussion process.

Sensitisation

Exposure to chemicals may result in a variety of allergic reactions among which allergic contact dermatitis (ACD) and sensitisation of the respiratory tract are those of greater importance because of their increasing prevalence.

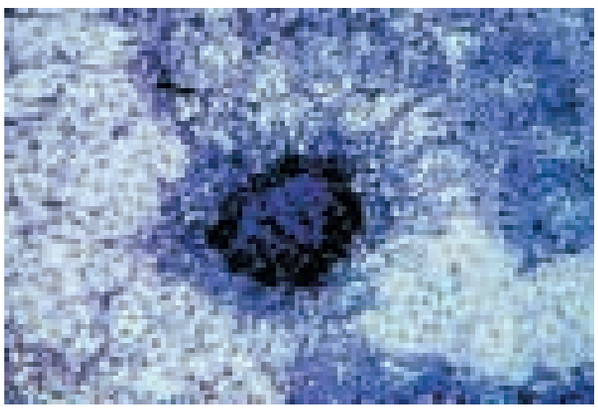
In the field of skin sensitisation progress has been made with the regulatory acceptance of the local lymph node assay (LLNA). However, the assessment of the sensitising potential of chemicals and products still relies on animal tests.

A task force on skin sensitisation was established in 2003 to decide on the best way forward in the identification of the most relevant endpoints, development, and pre(validation) of alternative test methods for skin sensitisation with the ultimate goal to validate a test strategy for the full replacement of the animal tests. In-house research activities are planned and a task force on respiratory sensitisation will be established in 2004.

Carcinogenicity

The detection of carcinogenic chemicals still remains a challenge, in particular in the case of substances that act via a non-genotoxic mechanism. To date no *in vitro* test that detects non-genotoxic compounds has been validated and accepted by regulatory authorities.

The objective of the activity on carcinogenicity is to set up a testing strategy to pick up genotoxic and non-genotoxic carcinogens. In the frame of these activities both **1)** classical methods (e.g. cell transformation assays and micronucleus test) are currently evaluated for their validity, and **2)** novel technologies, such as toxicogenomics will be used and evaluated.



Cell transformation assay 'Arsenito'

A taskforce has been created to steer all activities in this field from the organization of workshops and conferences to the development of collaborative networks with scientists from academia, industry and regulatory bodies.

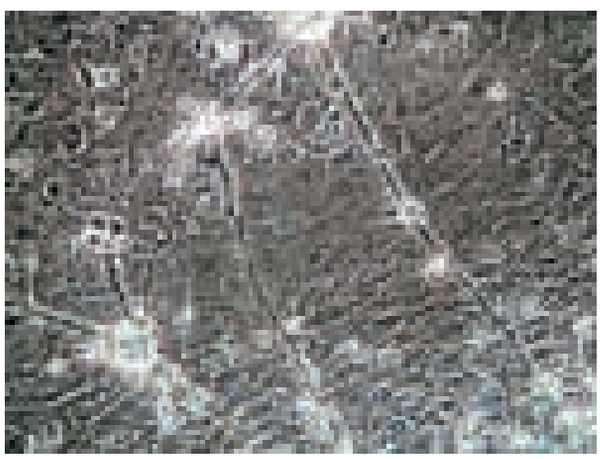
In the context of an integrated strategy based on the use of cell transformation assay by mouse fibroblast (Balb/3T3) in combination with genotoxicity *in vitro* testing (Micronuclei and Comet assays) extensive research work is ongoing, especially in the area of metal carcinogenicity. Moreover, ECVAM has started to explore in house and through collaborative studies the molecular signatures of a set of key carcinogenic chemicals, using both murine and human cells as target.

Reproductive Toxicity

ECVAM has finalized its activities in the area of using genetically engineered murine embryonic stem cells for the detection of teratogenic compounds. ECVAM is now focusing on the establishment of human embryonic stem cell technology in its laboratories. The potential of human embryonic stem cells to differentiate into all kind of cell types of the human body offers the unique opportunity to develop humanized in vitro tests which will avoid interspecies variations and will therefore enhance the predictivity of safety toxicological tests.

In addition, ECVAM has taken the lead to establish a consortium of about 30 partners to develop *in vitro* tests that can be used as building blocks in future testing strategies with the aim to detect reproductive toxicants. The integrated project proposal (ReProTect) has been granted by DG RTD and started on the 1st of July 2004.

ECVAM has strengthened its activities in the area of endocrine disrupters. A task force has been established and the ongoing OECD validation study on the Hershberger tests as well as the finalized validation study of the uterotrophic tests have been peer reviewed. ECVAM's reports have been submitted to the OECD. (Pre)validations of in vitro and in silico alternatives are under preparation.



Human neurons cultured at ECVAM

Toxicokinetics

Barrier function is an important determinant of absorption and distribution of compounds within the body. *In vitro* models are under evaluation to assess the passage of chemicals across biological barriers. A study on the standardisation of an *in vitro* model of intestinal barrier function has finished. An ongoing PhD study is developing and refining a test system for the blood-brain barrier (BBB).

A PhD project in the area of BBB is evaluating the possible replacement of primary glial cells in the current co-culture in vitro model by a glial cell line. The damage induced by lipoteichoic acid (LTA), which is involved in the pathogenesis of the bacterial meningitis, on BBB is also studied.

Ecotoxicology

As a follow-up of the ECVAM workshop on the use of fish cells in ecotoxicology (report 48 published in 2003), ECVAM created the new key area ecotoxicology and established a steering group, which at present focuses on reviewing the status of currently available *in vitro* systems with regard to their development and/or readiness for prevalidation/validation. Whether *in vitro* tests employing fish cells could replace the acute fish test, or at least reduce the number of fish needed, is being investigated.

Quantitative Structure Activity Relationships (QSARs)

Under current EU legislation for chemicals and chemical products, the use of (Q)SARs is limited, mainly because there has been disagreement in the scientific and regulatory communities over the applications of (Q)SARs, and the extent to which QSAR estimates can be relied upon. However, under the REACH (Registration, Evaluation and Authorisation of CHemicals) system, proposed initially in the Commission's White Paper on a Future Chemicals Policy and subsequently in the Commission's legislative proposal of 29 October 2003, it is anticipated that (Q)SARs will be used more extensively, in the interests of time- and cost-effectiveness and animal welfare. In particular, (Q)SARs are likely to play an important role in the assessment of chemicals produced or imported in quantities between 1 and 10 tonnes, for which minimal animal testing is foreseen.

In 2003, the JRC established networks of collaborators in the (Q)SAR field, and contributed to the OECD Activity on (Q)SARs, especially in relation to the evaluation of principles for the development and validation of (Q)SARs. The JRC was also involved in hosting the first OECD Workshop on (Q)SAR in March and in the scientific organisation of an OECD Workshop on the *Development and Use of Chemical Categories in the HPV Chemicals Programme*, which was held in Brussels in January 2004.

Biologicals

Biologicals are products such as vaccines, immunosera, immunoglobulins, hormones, monoclonal and polyclonal antibodies, which undergo extensive quality control during their production often involving tests on animals.

In 2003, the work on Three Rs approaches in the quality control of biologicals was continued and several working groups were established (steering group on biologicals, task forces on pyrogenicity and shellfish toxin testing). Three alternative methods for the potency testing of human tetanus vaccine and erysipelas vaccine, which have been validated in cooperation with other organisations, have been accepted by the regulators and incorporated into the European Pharmacopoeia. After successful finalisation of the validation study on in vitro methods for pyrogenicity testing a press conference was held and the compilation of the dossiers for the peer-review process was initiated. The workshop report on Three Rs approaches in the quality control of rabies vaccines was published. ECVAM continued to submit comments on revision proposals of European Pharmacopoeia monographs and European guidelines to promote the Three Rs concept in the quality control of biologicals.

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

Strategic Developments

ECVAM has taken a leading role in safeguarding quality control for in vitro studies including the application of the principles of OECD Good Laboratory Practice (GLP) to in vitro toxicological studies. In May 2004, the OECD Joint Meeting has approved the Advisory Document on "The Application of the GLP Principles to *in vitro* studies". Furthermore, ECVAM pursues its activities towards Good Cell Culture Practice (GCCP) guidelines, in order to reduce uncertainty in the development and application of in vitro procedures, by encouraging the establishment of principles for the greater international harmonisation, rationalisation and standardisation of cell and tissue culture based laboratory practices. ECVAM has recently published in (December 2002) a task-force report and is now preparing a Guidance Document on GCCP.

Toxicogenomics will be exploited as a second generation of alternatives and will be applied mainly in areas where no satisfying alternatives exist. A workshop on the principles of validating toxicogenomic approaches was held in December 2003 and a pilot in vitro study involving industry and a technology provider was carried out to identify the potential of these technology methods for regulatory purposes when applied to in vitro biological systems on carcinogenic substances.

Another challenge will be to use automated cell and tissue approaches. A concept to set up an automated in vitro test laboratory for acute toxicity testing (also part of the Integrated Project A-Cute-Tox) has been developed, which shall in conjunction with a depository of chemicals allow to produce larger standardised data sets on in vitro toxicology systems as well as optimise the performance of all tests.

Scientific Information Service (SIS)

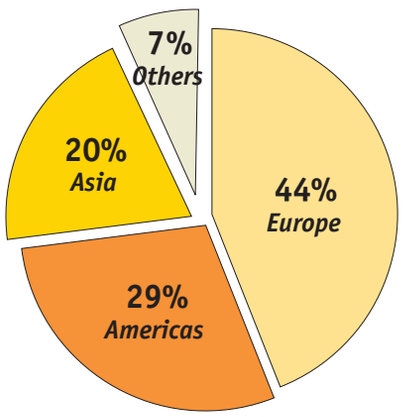
In line with its institutional duties, ECVAM maintains a scientific information service (**http://ecvam-sis.jrc.it**, SIS) to disseminate factual and evaluated (ready-to-use) information on advanced alternative methods for toxicology assessments. In addition to the SIS databases, as the core application, SIS includes the *ECVAM Thesaurus* and the *ECVAM website*.

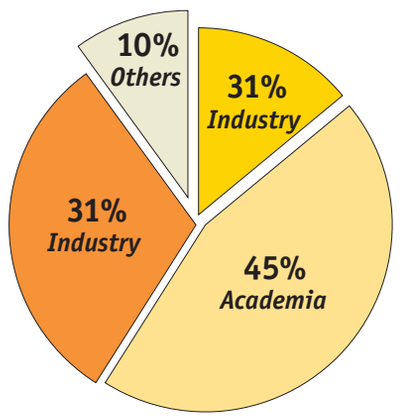
The year 2003 has seen a considerable increase in the total information content of the SIS databases, doubling the information compared to 2002. The USA, UK and India are currently the biggest customers of SIS.

Information Sector	Data Sheet Number
Method Summaries	39
INVITTOX Protocols	128
Evaluation/Validation Studies	17
Test Compounds	1.198
Test Results	4,219
Bibliographic References	2.452

SIS data coverage

SIS Users Origin





Profile of SIS Users

Total: 2940 registered users from 65 countries (May 2004)

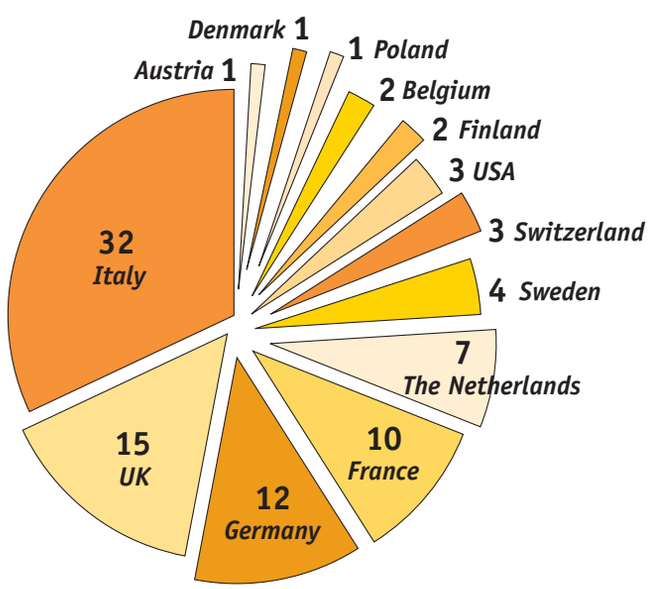
The ECVAM Thesaurus, a systematic collection of harmonised terms in the animal alternatives area, is a result of a collaborative project with the US National Library of Medicine (NLM). Online distribution is expected in 2004.

The ECVAM website became an interactive information service in 2003 supporting the management of international meetings organised by ECVAM and it has been complemented with an easy-to-use registration procedure that allows external interested parties to be regularly updated on the latest news of ECVAM.

NETWORKING

ECVAM established 11 key areas directly targeting the animal experiment to be replaced with the support of international working groups with participation of stakeholders and international experts.

ECVAM collaborates in 15 Networks in the form of Task Forces on Acute fish toxicity, Biocompatibility testing, Blood-brain barrier, Carcinogenicity, Endocrine Disrupters, Good Cell Culture Practice, High-throughput screening, Metabolism, Neurotoxicity, Pyrogenicity, (Q)SARs, Sensitisation, Shellfish toxin testing, Skin Irritation, Toxicogenomics and Biologicals. In total, 99 members from 14 countries (distribution see the figure) are collaborating and disseminating information on tightly defined tasks.



ECVAM Task forces (Country distribution)

The activities on in vitro tests and QSARs involve, furthermore, consultation with, and dissemination of in-

formation through, the following networks: OECD Networks (the OECD Expert Group on (Q)SARs, the OECD Validation Management Group For Non-Animal Testing (VMG Non-Animal), the OECD Existing Chemicals Task Force, the OECD Working Group of National Coordinators of the Test Guidelines Programme, the OECD Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology. Furthermore, a close collaboration with the American counterpart ICCVAM was set up including a mutual observer status and various joint workshops, taskforces and studies.

Enlargement

ECVAM organised a practical training course on in vitro methods for pyrogenicity testing in Hungary and a workshop on alternatives to the use of animals in higher education in Poland.

Two PhD students from Candidate Countries are currently working at ECVAM on the development of structure-activity relationships for pharmacotoxicological endpoints and on the development of in vitro testing methods for assessment of neurotoxic and neurodegenerative potential.

A scientist from Poland worked at ECVAM for a period of six months in the key areas Systemic Toxicity and Strategic Developments.

Patent

EP patent application on "Functionalization of intracoronary stents" (EP n° 02292525.9)

Competitive Activity

Participation in the Executive board of PREDICTOMICS (STREP project "Short-term in vitro assays for long-term toxicity").

Two applications for Integrated Projects were steered by ECVAM (A-Cute-Tox and ReProTect) and will start in 2004.

Prizes / Awards

Thomas Hartung was granted a honorary professorship at the University Konstanz, Germany and the Award for Environment and Society by LBS Baden-Württemberg, Germany.
The US Environmental Protection Agency (EPA) has nominated Andrew Worth as an expert consultant in a newly-established Panel of the EPA Scientific Advisory Board on Computational Toxicology.

ECVAM Workshops & Task Forces

In 2003, ECVAM organised eight meetings on Biologicals, Endocrine Disrupters, Good Cell Culture Practice (GCCP), Metabolism, Neurotoxicity, Pyrogenicity, Sensitisation and Skin Irritation. Five workshops were held on the Validation principles for toxicogenomics-based test systems, Strategies for non-animal acute systemic toxicity testing, Possible applications of *in vitro* blood-brain barriers models, Skin irritation validation study and *In vitro* systems for evaluating immunotoxicity. Furthermore, international working group meetings were organised for the purpose of the Cosmetics Directive.

Two reports of ECVAM workshops on ecotoxicology and the quality control vaccines were published.

Major Events

The 1st Meeting of the OECD Expert Group on (Q)SARs was organised and hosted by the JRC in March 2003. During this meeting, a proposal was developed for the QSAR Activity. It was adopted in June 2003 by the OECD Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology.

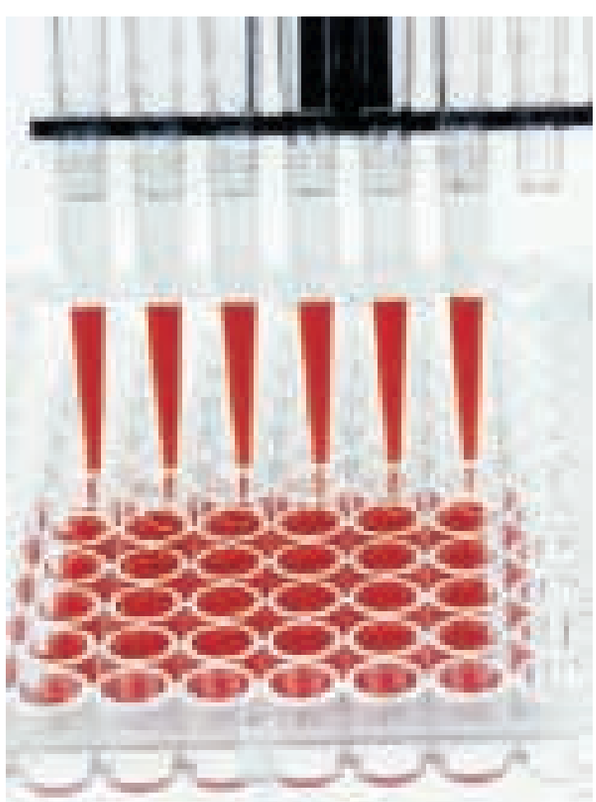


Image from the Pyrogenicity study

Press Conferences

In a press conference in May 2003 European Commissioner for Research Philippe Busquin presented the results of the EU-funded validation study that demonstrated that a few human blood cells are able to eliminate animal testing for parenteral (non-oral) drugs. In collaboration with DG Research ECVAM has successfully evaluated six blood cell methods for monitoring side effects such as fever reactions arising from contaminants of injectable drugs. This could avoid the need to test on about 200,000 laboratory rabbits per year in Europe.

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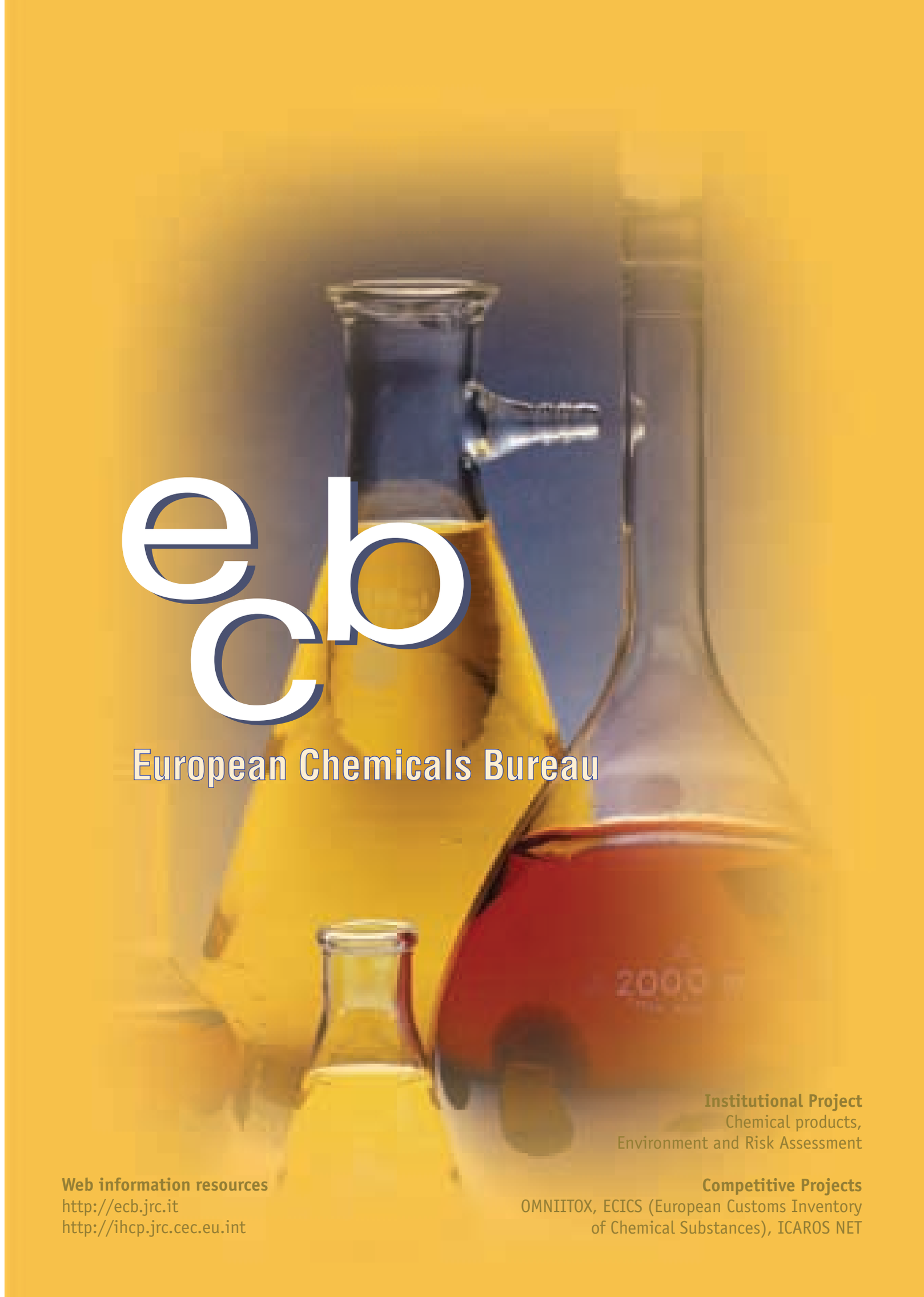


Institutional Project
Chemical products,
Environment and Risk Assessment

Competitive Projects
OMNIITOX, ECICS (European Customs Inventory
of Chemical Substances), ICAROS NET

Web information resources
http://ecb.jrc.it
http://ihcp.jrc.cec.eu.int

European Chemicals Bureau (ECB)

The ECB provides scientific and technical support to the conception, development, implementation and monitoring of EU policies on dangerous chemicals. The aim of the legislation is to ensure a high level of protection for workers, consumers and the environment against dangerous chemicals and to ensure the efficient functioning of the internal market on chemicals under the current Community legislation. The ECB ensures the development of methodologies and software tools to support a systematic and harmonised assessment of chemicals addressed in a number of European directives and regulations. The activities of the ECB are executed in close co-operation with the relevant authorities of the EU Member States and Norway, Commission services (such as DG Environment and DG Enterprise), the chemical industry, the OECD and other international organisations, and NGOs.

REACH

The IHCP has responded to the needs set out by the REACH (Registration, Evaluation and Authorisation of CHemicals) system. The European Chemicals Bureau (ECB) contributed extensively to the drafting of the REACH legislation, specifically the technical annexes. The ECB also produced an important report on the testing needs under REACH and on the role of (Q)SARs (Quantitative Structure Activity Relationships). (Q) SARs can play an important role in reducing the testing needs (and costs) for industry under the future REACH legislation. An international workshop on the scientific aspects of REACH was organised in December, 2003 by IHCP.

CLASSIFICATION & LABELLING

The ECB is in charge of the technical and scientific issues for Adaptations to Technical Progress (ATP) of Annexes I, II, III, IV, VI and IX to Council Directive 67/548/EEC on the classification, packaging and labelling of dangerous substances. The work comprises mainly of the preparation, chairing and follow-up of the meetings of the Commission Working Group on Classification and Labelling, co-ordination between Member States and Industry of discussions and activities between meetings, and providing information to other Commission Services.

The single most important achievement of the work on C&L was the preparation of the draft 29th Adaptation to Technical Progress to the Directive including an update of the list of classified substances in Annex I, which was sent to DG ENV at the end of the year. It contained about 900 revised or new entries to Annex I.

General issues discussed by the Working Group during the year:

- Discussion on the New Chemicals Policy and the possible implementation of the Globally Harmonised System (GHS) on classification and labelling.
- How to work during the interim period.
- Discussions on parental toxicity in relation to fertility and developmental effects
- Testing the GHS criteria for classification and labelling for substances classified under the current system.
- Haemolytic effects related to classification with R48.
- Classification of substances that may emerge as aerosols.
- Continued discussion on potency of sensitising substances.
- Issues concerning the 29th ATP.
- Classification of metals and metal compounds from the ESR programme.
- Specific concentration limits for environmental classification.

About 40 substances were evaluated in the Pesticides group for health effects and about 30 substances were evaluated for environmental concerns.

EXPORT / IMPORT

The ECB fulfils the duties of the Commission within the export notification process as laid down in Regulation (EEC) 304/2003. It gives technical and scientific support for the implementation of the Regulation, which aims at:

1. Implementing the EU export notification procedure,
2. Making the voluntary UNEP/FAO Prior Informed Consent (PIC) procedure legally binding within the Community and
3. Using the same rules for classification, packaging and labelling outside the Community that apply in the internal market.

162 export and import notifications were carried out in accordance with the new Regulation that entered into force in February 2003. The European Database on Export and Import – EDEXIM was upgraded to meet the requirements of the Regulation. The ECB continued to contribute to a project to create an international platform for capacity building, mainly based on Internet applications under the IFCS.

Export Notifications							
1996*	1997*	1998*	1999*	2000*	2001*	2002*	2003*
23	7	6	2	3	2	2	162

** Under Regulation 2455/92, repealed by Regulation 304/2003*
***Under the new yearly export notification system under Regulation 304/2003*

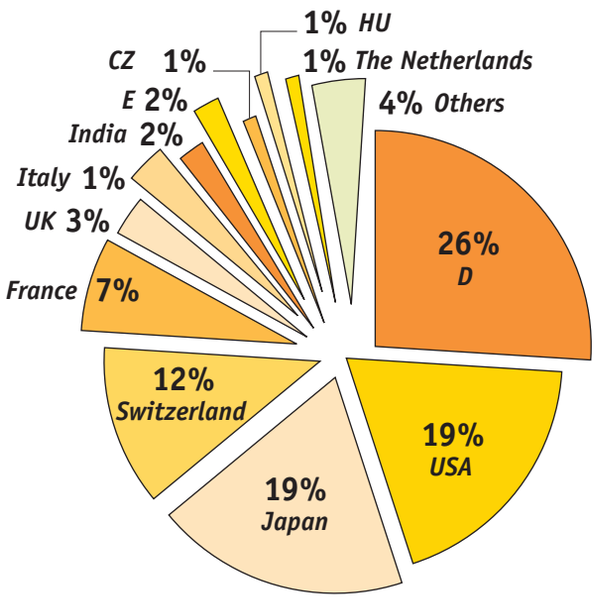
TESTING METHODS

The ECB is responsible for the technical/scientific work needed for the development, introduction and adaptation to technical progress (ATP) of testing methods of Annex V to Dir. 67/548 (and its adaptations).

In order to ensure a harmonisation of test methods in as a wide international context as possible, according to the principle of Mutual Acceptance of Data, the Commission participates in the OECD Test Guidelines Programme by promoting and proposing the development and adoption of new Test Guidelines needed under EU legislation on chemicals control. Subsequently, adopted guidelines are adapted and introduced into Annex V. The ECB coordinated the introduction of projects for two new guidelines in the OECD Programme in 2003. In addition, the preparatory work for the foreseen 29th ATP has continued and thirteen methods (including translations to all official languages) were provided to DG Environment. First drafts in Annex V format of several additional methods were prepared. Complete final adoption in OECD is, however, necessary before proceeding to finalise them and subsequently circulate them to the National Coordinators for comments and agreement.

NEW SUBSTANCES (Directive 67/548/EEC)

Over 6000 notifications in total, including nearly 4000 new chemical substances, have been submitted since 1983, in the recent years equivalent to 350–400 notifications and 250–300 substances per year. Irrespective of notification date, in the last years a similar number of notifications have been processed annually by ECB (in 2003: 879 dossiers, comprising 493 notifications and 386 updates). High priority was given to availability of information via the ECB internet pages. A 7th edition of ELINCS (European LIst of Notified Chemical Substances) in English has been made available through the ECB Web site.



Origin of substances notified in 2003

EXISTING SUBSTANCES

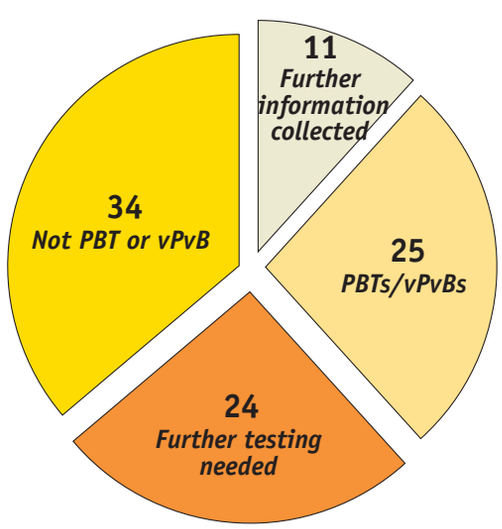
The Regulation 793/93 foresees that the evaluation and control of the risks posed by existing chemicals, i.e. the ones listed in the European Inventory of Existing Commercial Substances (EINECS), an inventory containing 100,106 substances, will be carried out in four steps: (1) data collection, (2) priority setting, (3) risk assessment and (4) risk reduction. In providing scientific support to the implementation of the Regulation, the ECB aligns its work with the strategy for implementing an environmentally sound management of toxic chemicals outlined in Chapter 19 of the Agenda 21 Rio Declaration, adopted at the UNCED in 1992, and reaffirmed in Johannesburg 2002. On the international level, the ECB is thereby responsible for scientific and technical inputs to the OECD existing chemicals programme and several UN initiatives on chemicals.

By the end of 2003, the total number of EU high production volume substances is 2747, this is an increase of 43 HPVs over the previous year. The total number of low production volume chemicals is decreased from 7842 to 7829, as a result of 13 becoming categorised as HPVs.

In 2003, all the non-confidential data were placed on the ECB Website in downloadable IUCLID pdf format. In

addition, the full IUCLID (International Uniform Chemical Information Database) installation (software, Oracle licence and data CD) was distributed to the nominated Authorities in the 10 EU Accession States. Furthermore, user requirements for IUCLID 5.0 were developed and work on defining the technical specifications of the software started in 2003 in order that programming can commence in 2004. In addition, the ECB contributed to the development of the global portal for exchange of data on HPV chemicals under the auspices of OECD in the frame of an EU/US initiative. In support to the EU enlargement, a IUCLID course was given in October 2003 in Bratislava (Slovakia). The course was highly appreciated by the participants from the competent authorities in the new Member States. More courses are scheduled in 2004. In order to facilitate the correct use of IUCLID 4.0, Guidance Documents are being drafted in the frame of a joint collaboration with CEFIC.

In terms of priority setting, during 2003, our work on identifying potential Persistent, Biocumulative and Toxic substances continued. Potential PBTs were evaluated by a Member State, industry and NGO Expert Working Group over 3 meetings hosted and chaired by ECB. Substance fact sheets were updated with additional information provided in the main by Industry. Substances were either verified as PBT/vPvB, deleted from the list or identified as requiring further testing. This work will continue in 2004.



Results of the categorisation of the 94 substances on the potential list of PBTs

In April 2003, under the OECD/JRC cooperation the ECB hosted the first meeting of the Ad-hoc expert group on Quantitative Structure-Activity Relationships ((Q)SARs). In relation to the increased emphasis on QSAR development and validation under REACH the QSAR activity was re-established in 2003 in ECB as Key Action under the EU 6th Framework Program of Research. This activity was transferred to ECVAM mid year, but the ECB maintained and will continue to maintain close links with the activity in 2004 in preparation of guidance documents on testing requirements for REACH. ECB participates in the OECD Expert Group on (Q)SARs and the ECVAM Task Force on QSARs.

The main results regarding risk assessment by the ECB are summarized here below:

- Discussions were started on 21 substances at Technical Meeting (TM) level
- Discussions were completed on 5 substances at TM level
- Draft reports were finalised on 16 substances and sent to CSTEE
- RARs on 15 substances were published on the ECB Website (modification in the light of CSTEE opinion, formatting and editing)
- The preparation for publication of the results of the work of the TM in one Commission Recommendation and a Commission Regulation on testing requirements under Article 10.2.

Significant effort has been made to upgrade and maintain up-to-date Web-based communication via the ECB web site. All the online information can be found via the following URL address: **http://ecb.jrc.it**. The ECB Website is now well known and the 35 M monthly visited pages as well as the 2000 unique users/day are reached.

BIOCIDES (Directive 98/8/EC)

The ECB is in charge of the scientific and technical issues raised in the approval of active substances in biocidal products as laid down in Directive 98/8/EC. For 2003 the main task has been to complete the notification phase, which is the basis for Annex II of the Second Review Regulation.

The evaluation of the active substances will start in 2004 and, including 2003, the main tasks of the work area have been to give support to the Competent Authorities on the guidance documents for the implementation of the Directive and priority setting in the review programme. These tasks will continue, but the emphasis will change in the direction towards harmonisation of the evaluation process for the substances in the review programme.

The work area acts as a Help-Desk for the Biocides Directive and the Review Regulations where there is a growing need for information and the work area has daily telephone and e-mail information requests to answer.

In preparation of the review programme the following tasks were undertaken in 2003:

- The final lists of all existing active substances used for biocidal purposes were generated as well as the list of notified substances and product types. These lists are the main content of the 70 pages annex to the second review regulation that was published in the Official Journal of the European Communities 3rd November 2003. Rapporteur member states were allocated to substances on the first two priority lists.
- The User's guidance for the TNsG on Human Exposure to in Biocidal Products was progressed and is expected to be finalised early 2004.
- The Technical Guidance Document on Risk Assessment was published.
- The Emission Scenario Documents (ESD) for product type (PT) 5 (Drinking water disinfectants), PT 10 (Masonry preservatives), PT 11 (Preservatives for liquid cooling systems), PT 12 (Slimicides), PT 13 (Metal working fluids), PT 14 (Rodenticides), and PT 15 (Avicides) were finalised.
- A course on using the ESD for Wood Preservatives and Rodenticides was held for the authorities of the member states.
- The working group on data requirements and testing strategies held its first meeting resulting in better-defined specific data requirements for rodenticides, especially regarding the long-term tests for anticoagulants.
- A course on IUCLID targeting the accession countries was held.
- The biocides team participated in numerous events and conferences aiming at explaining the Biocides Directive, the first and second review regulations and consequences.
- The web page for Biocides, **http://ecb.jrc.it/biocides**, has continuously been up-dated, to enable industry to check that their information is registered correctly and to distribute information to third parties.

For the Biocides, a detailed description of Exposure both for the Environment and for Humans is crucial for the understanding of the risk. In order to assure adequate guidance on this matter DG ENV tendered for a continuation of the project on environmental exposure scenarios, EUBEES. The EUBEES II project held 3 meetings during 2003 where draft reports on development, harmonisation or testing of Emission Scenario Documents for a number of product types were evaluated. The user's guidance report on models for human exposure to active substances in biocidal products was further progressed.

Main achievements in 2003:

- The Second Review Regulation (RRII), Regulation (EC) No. 2032/2003, was published.
- Update of the TNsG on data requirements for PT 14 (Rodenticides).
- The TGD revision for the Risk Assessment of New Notified, Existing Substances and Biocides was published.
- For the Environmental Exposure, EUBEES II was finalised, resulting in Emission Scenario Documents for 7 more product types.
- Biocides Notification and Identification Scheme: Regulation EC No. 1687/2002, with a legal deadline of 31 January 2003, resulted in about 50 additional notifications which were loaded into the database and checked, and subsequently registered in the list of notified substances in RRII where relevant.
- The allocation of Rapporteur Member States for the 1st and 2nd priority lists was finalised, and the allocation for the 3rd and 4th priority lists has been initiated.
- Further development of the formats for submission of Robust Study Summaries based on the TNsG on Dossier Preparation for biocidal active substances and biocidal products were initiated.
- The ECB has carried out 2 training courses one regarding Emission Scenarios for Rodenticides and Wood preservatives, and one IUCLID course for the accession countries.

COMPETITIVE ACTIVITIES

OMNIITOX project (EC project number: G1RD – CT2001 – 00501)

The project OMNIITOX (Operational Models aNd Information tools for Industrial applications of eco/TOXicological impact assessments) aims to enhance the capability of industry to select more environmentally benign chemicals and processes. A feasibility study on introducing elements and concepts of the Life Cycle Analysis framework into the regulation of chemicals has taken shape during 2003.

ECICS – European Customs Inventory of Chemical Substances (TAXUD/2002/DE/305)

Directorate General for Taxation and Customs Union (DG TAXUD) and the JRC have established the ECICS feasibility study. The ECICS database compiles internationally marketed chemicals in an unequivocal manner for customs and legal purposes. It contains about 35,400 chemical names (corresponding to approximately 28,600 chemicals) in the 11 Community languages, with the customs classification in the CN, the CAS number and the CUS (Customs Union and Statistics) number. The ECICS feasibility study started in October 2003 and will assess the feasibility of updating the ECICS database.

ECB SELECTED PUBLICATIONS IN 2003

ASCHBERGER, K., CHYLA, M.A., PEDERSEN, F., PAYA PEREZ, B.A., RASMUSSEN, K. "Identification of Substances of Very High Concern among Biocides". *13th Annual Meeting on Understanding the Complexity of Environmental Issues. A Way to Sustainability,* SETAC Europe, 27 April - 1 May 2003, Hamburg (D) - ORA 63542

CHRISTENSEN, F.M., DE BRUIJN, J., HANSEN, B.G., MUNN, S.J., SOKULL-KLUETTGEN, B., PEDERSEN, F. "New Assessment Tools under the New EU Chemicals Policy". *Greener Management International,* Vol. GMI 41 (2003) 5-19 - ART 91459

CHRISTENSEN, F.M., OLSEN, S.I. "The Potential Role of Life Cycle Assessment in Regulation of Chemicals in the European Union". *SETAC Europe 13th Annual Meeting,* 27 April - 1 May 2003, Hamburg (D) - ORA 63508

CHRISTENSEN, F.M. "Human Exposure Assessment. General Principles and Regulatory Aspects. Risk Assessment for Chemicals and Biocidal Products", *IBC,* 10-11 June 2003, London (U.K.) - ORA 63856

CHRISTENSEN, F.M., DE BRUIJN, J., PEDERSEN, F. "REACH and Information Exchange in the Chemical Supply Chain". *Seminar on Chemicals and Communication,* CETOX, 23 September 2003, Copenhagen (DK) - ORA 64227

CRONIN, M.*, JAWORSKA, J.*, WALKER, J.*, COMBER, M.*, WATTS, C.*, WORTH, A. "Use of QSARs in International Decision-Making Frameworks to Predict Health Effects of Chemical Substances". *Environmental Health Perspectives,* Vol. 22 (2003) 1391-1403 - ART 91265

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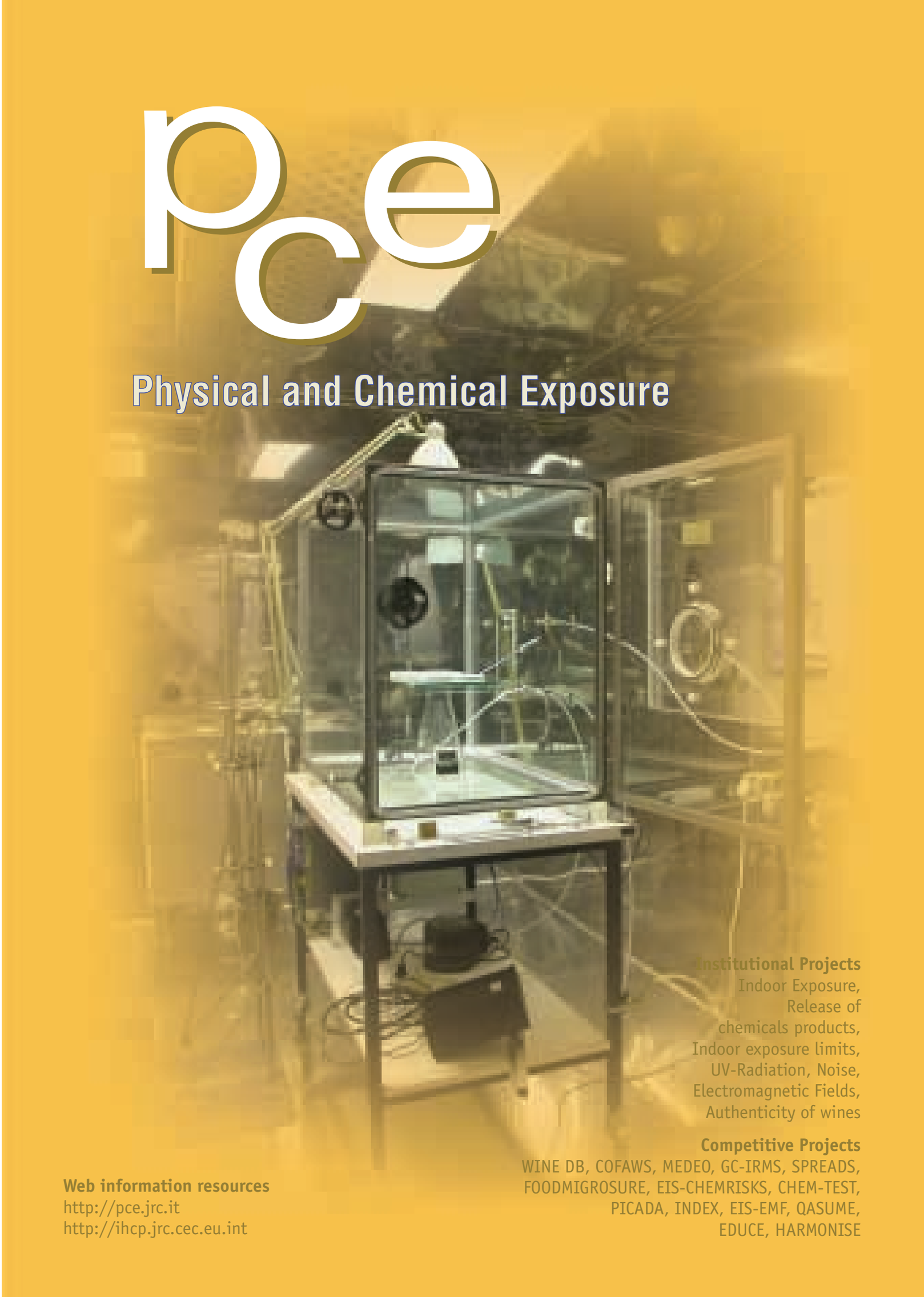
pce

Physical and Chemical Exposure



Institutional Projects
Indoor Exposure,
Release of
chemicals products,
Indoor exposure limits,
UV-Radiation, Noise,
Electromagnetic Fields,
Authenticity of wines

Competitive Projects
WINE DB, COFAWS, MEDEO, GC-IRMS, SPREADS,
FOODMIGROSURE, EIS-CHEMRISKS, CHEM-TEST,
PICADA, INDEX, EIS-EMF, QASUME,
EDUCE, HARMONISE

Web information resources
http://pce.jrc.it
http://ihcp.jrc.cec.eu.int

Physical and Chemical Exposure Unit (PCE)

The Unit provides scientific understanding, information and assessment tools to support the Commission services in evaluating and quantifying human exposure and risk assessments for environmental stressors. Stressors include chemicals, UV-radiation, electromagnetic fields and noise.

There is clear evidence among experts and policy makers that the lack of human exposure data represents a major bottleneck in the risk assessment process. This has also been recognised by the EU Council of the Environmental Ministers, which requested the EU Commission to undertake action for eliminating existing deficiencies in exposure data. Responding to this challenge, the overall objective for the PCE Unit is to develop infrastructure, tools and reference data to enable harmonised exposure assessment procedures in the EU, and to support the implementation of key policies and directives, such as:

- New Chemicals Policy: REACH (Registration, Evaluation, Authorisation of Chemicals)
- General Product Safety Directive (GPSD) (2001/95/EC)
- Food contact materials (e.g. 82/711/EEC, 85/572/EEC, 89/109/EEC, 90/128/EEC, 93/11/EEC, 2001/61/EC, and related amendments)
- Textile fibres (96/74/EC, 97/37/EC, 96/73/EC, 73/44/EEC)
- EU Tobacco Directive (2001/37/EC)
- Indoor exposure limits for priority pollutants (INDEX)
- Authenticity of wines (EC regulation 2729/2000, Regulation (EEC) N° 2081/92, Regulation (EEC) N° 2082/92, EC Reg N° 2870/2000, EC Reg N°440/2003)
- Noise Directive (2002/49/EC)

During the last five years exposure assessment to chemicals and physical stressors and in particular, the characterisation and estimation of emissions and the release/migration of chemicals from consumer products and food contact materials has received much attention. The PCE Unit has focused its activities on the following areas:

- Sources and Routes of Exposure to Chemicals and Physical Agents
- Consumer Exposure Modelling
- In vivo / In vitro Evaluation of Effects
- Modelling of Noise Propagation
- Establishment of an Information System on Electromagnetic Fields and
- UV Radiation Measurements

In line with the priorities of FP 6 and in support to Commission services the Unit has developed for the period 2003-2006 three actions:

1 **Total Human Exposure Assessment Studies (THEXAS Chem)** The objective of THEXAS chem is to evaluate the risk for European citizens deriving from the overall exposure to chemicals through different routes (air inhalation, skin contact etc.) occurring in indoor and occupational environments.

2 **Total Human Exposure Assessment Studies (THEXAS Phys)** THEXAS Phys has the objective to evaluate population exposure to physical agents (UV-radiation, noise, electromagnetic fields-EMF) and

3 **European Office for wine, Alcohol and Spirit Drinks (BEVABS)** BEVABS manages the European Data Bank on authentic European wines (EC regulation 2729/200) and to coordinate the Network of official Member States laboratories involved in Nuclear Magnetic Resonance (NMR) determinations required for the databank. In the past years, BEVABS has carried out the development and validation of the method for the determination of the $^{13}C/^{12}C$ isotope ratio of ethanol, which has been adopted at International level by the Office International for Wine and Vine (OIV) and in March 2003 as official method by the European Union (EC Reg 440/2003). A scientific highlight of 2003 was the second International Symposium on Isotopomers (ISI 2003, **http://ihcp.jrc.cec.eu.int/EVENTS/ISI2003/isi2003.html**).

The integration of the activities of these actions into a coordinated work-program allows the PCE Unit to apply a holistic approach to human exposure, i.e. estimates and assessment via different routes of exposures to chemicals and physical agents as the basis for the development and implementation of a "European Exposure Assessment Toolbox", which includes:

- common measurement methods and protocols,
- reference exposure data (chemicals/agent specific),
- reference exposure factors (non-chemical specific, such as anthropometric data, time/activity patterns, etc.),
- reference exposure-associated health data,
- common exposure models,
- exposure assessment guidance documents,
- reference exposure scenarios.

The "European Exposure Assessment Toolbox" offers the emerging "REACH Implementation Plans" (RIPs) initial pilot exercises and support on downstream user issues.

ACTION THEXAS CHEM

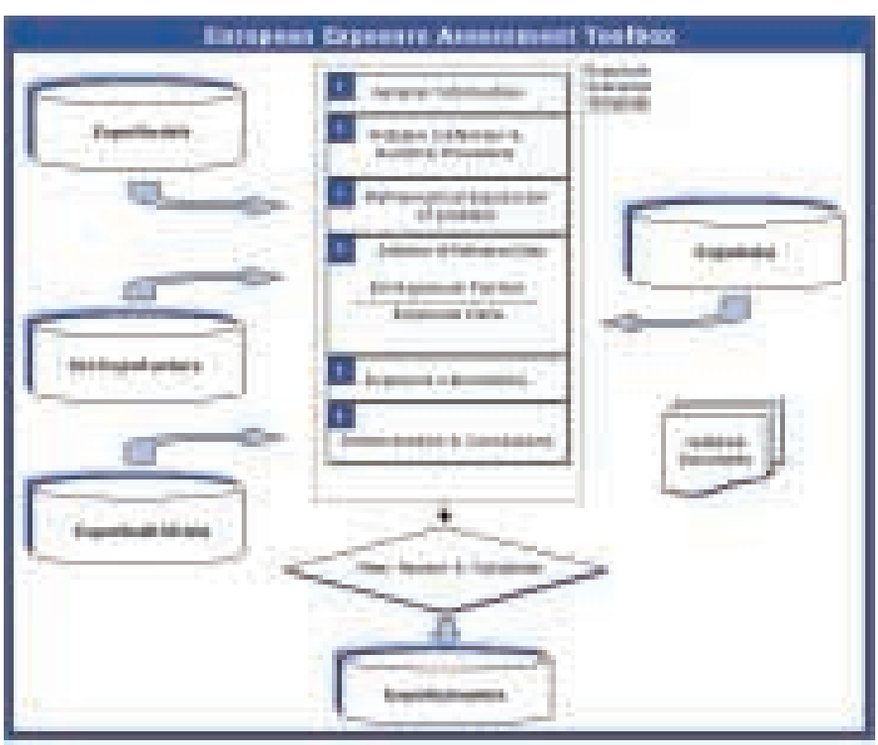
The EU Environment Council has put forward a request to the European Commission to undertake action for eliminating existing deficiencies in data on human exposure to chemicals. In this light, JRC is developing methods and tools to accurately evaluate the risk for European citizens deriving from the overall exposure to chemicals through different routes (food intake, air inhalation, skin contact, etc.) occurring in indoor and occupational environments. In the frame of this action human exposure is seen a holistic approach, which includes estimates and assessment of exposures to chemicals released from products and articles (e.g. VOC, phthalates, biocides, dyes etc.) as the basis for the development, testing and implementation of:

- Common measurement methods and protocols
- Common exposure models
- Exposure assessment procedures and tools
- advanced biomarkers/metabonomic exposure analysis and assessment concepts,
- potential interactions of "physical/chemical cocktails".

The work will be carried out in dedicated laboratories of the PCE Unit specialised in the different types of analytical tools, exposure set-ups and exposure pathways to chemical and physical agents:

- Indoortron Laboratory: mainly inhalation exposure research
- Migration research / contact materials Laboratory: mainly oral and dermal exposure research
- Toxicogenomics Laboratory: chemical mixtures / cocktails / biomarkers research
- Action THEXAS phys UV (and Noise) Laboratories: cocktails research in co- operation with the toxicogenomics laboratory
- BEVABS/NMR laboratory: biomarkers / metabonomics research in co-operation with the toxicogenomics laboratory for characterising relevant arrays of biomarkers for specific exposures.

These laboratories are being developed to act in their respective areas as Reference Laboratories at EU level to improve the currently achievable quality and comparability of measured/modelled data related to consumer and occupational exposure. In particular, there is a specific request by DG SANCO to further develop the Migration research / contact materials Laboratory into a CRL in the area food contact materials.



The European Exposure Assessment Toolbox

In 2003, the following activities / projects were carried out:

EIS-ChemRisks / ChemTest

The objective is to support the implementation of the General Product Safety Directive and REACH by developing exposure assessment tools and reference data. To this end, a key activity in 2003 was the prototyping of the "European Exposure Assessment Toolbox" on the example of chemicals released from consumer products and articles. A prototype version was released. Main results of the project were presented in a dedicated workshop organised by the International Society for Exposure Assessment, ISEA 2003. Testing of the toolbox has been started on a sectorial basis, on textiles, toys and personal care products. Within this frame, policy options on the safety of tattoos and piercing were presented to DG SANCO.
(See project reports in **http://139.191.172.32/eis-chemrisks/documents.cfm**).

Harmonisation and validation of consumer exposure models

This activity acts as an interface for other important European projects, such as the CEFIC/LRI Exposure Factors Sourcebook project co-ordinated by KTL (Finland), the JRC EIS-CHEMRISKS project (funded by DG SANCO) and the CONSEXPO and EUSES projects. The ultimate goal is to harmonise and validate existing consumer exposure models with particular focus on those used in the EU, in particular

- to make an inventory of existing exposure models (with special focus on consumer exposure models)
- to identify harmonisation and validation needs for these models and
- to proceed with the harmonisation and validation of an appropriately selected subset of models based on well established specific exposure factors, data and scenarios.

In 2003 the Consumer Exposure Modelling Task Force (CEM TF) established a web-based inventory of existing exposure models **http://cem.jrc.it/cemdb/** with particular emphasis on consumer exposure models. This database was created on the basis of model fact sheets that have been prepared on the basis of information collected from different sources in EU and USA concerning: **(a)** existing exposure models; **(b)** exposure studies in EU/USA and models employed in them and **(c)** degree of exposure models verification and validation.

Food Contact Materials / Migration Processes

The activities on migration of chemicals from materials focus on experimental approaches to produce reliable data for exposure assessment and pre-normative purposes. They include development, comparison and validations of methods, exploratory research, monitoring surveys at EU level to quantify contaminants, databases on migrants and dissemination of information via websites, courses, and expert workshops. The work is performed in close collaboration with DG SANCO and DG ENTR, and fosters excellent contacts with international research organisations and concerned industries. The policies supported are on food contact materials (e.g. 82/711/EEC, 85/572/EEC, 89/109/EEC, 90/128/EEC, 93/11/EEC, 2001/61/EC, and related amendments), toys (1999/81/EEC, 76/769/EEC, 88/378/EEC, 92/59/EC), and textile fibres (96/74/EC, 97/37/EC, 96/73/EC, 73/44/EEC). The main achievements in 2003 are summarized in the following:

- In 2003, the structural development of the CRL continued with a focus on the quality program, which includes ISO 17025 accreditation and participation in proficiency tests on migration since 1997. The accreditation ISO 17025 first obtained in January 2003 was extended to another method.
- A stability study of Certified Reference Materials 537, 538, and 539 was completed for the Institute for Reference Materials and Measurements (IRMM). The results following ISO 17025 protocol for overall migration in olive oil by total immersion for 10 days at 40°C showed the continued adequacy of the CRMs.
- The results of the European Survey on migration levels of epoxidised soybean oil (ESBO), a plasticiser from closure gaskets from baby food jars was published and led to a request from the European Food Safety Authority (EFSA) to conduct the exposure assessment. The methodology developed for chlorohydrin-derivatives of ESBO in gaskets is being optimised for foodstuffs.
- Exploratory research in 2003 also focused on active packaging, which can interact with the internal gas environment to extend the shelf-life of a food. An investigation on industry prototypes is on-going with a focus on interactions and migration issues between these materials and food matrices.
- The work within the frame CEN TC194 (materials and articles in contact with food) continued. The working group on coatings has been conducting a validation trial, whereas the task group on amines is developing a confirmation method for the quantification of primary aromatic amines from multilayer materials.
- A new project was initiated in 2003 on behalf of DG ENTR to validate methods related to new generic names for textile fibres. The pre-validation of a method for the identification and quantification of a

new generic fibre polylactide was completed and showed adequacy.
- Horizontal collaborations with the project EIS-CHEM-RISKS have been initiated for textiles and toys.
- Events in 2003 included hosting the meeting of all working groups of CEN TC 194, organising a course for SMEs on diffusion modelling and one on active packaging.

European Indoor Air Monitoring and Exposure Assessment Study (AIRMEX)-Public Buildings

In the frame of the AIRMEX project (Indoor Air Monitoring and Exposure Assessment Study) measuring campaigns were carried out in Catania and Athens to estimate indoor/outdoor relationships and personal exposure concentrations for selected volatile organic compounds (aromatics, carbonyls, terpenoids). The measuring objects included public buildings (town halls, guild halls), schools and kindergartens. Personal exposure measurements were conducted with employers and/or teachers already working in the pre-selected working environments. It was found that generally the total VOC concentrations inside the buildings are higher and/or similar to the outdoor concentrations. In buildings located in the city centre there is almost no difference between indoor and outdoor pollutant levels. Almost always the personal exposure concentrations are higher than those indoors and outdoors indicating the presence of unknown sources for VOCs. The measuring campaigns will be continued in 2004, including cities in other European countries.

Toxicogenomics

Activities in the area of environmental toxicology in the last five years evolved from support to EU Strategy on Endocrine Disruptors and International co-operation, which produced the following milestones:

- WHO-IPCS Global Endocrine Disruptors Research Inventory (GEDRI), located at the JRC
- WHO-IPCS Global Assessment of Endocrine Disruptors (GAED), final report, 2002
- EU/US Transatlantic Co-operation in Human and Environmental Health on EDCs, Ispra April 2001
- Co-ordination of the research project EDAEP, Endocrine Disrupting Ability of Environmental Pollutants, founded by DG Research, 1995-1999
- WHO-IPCS Report on Integrated Risk Assessment, 2002

The current main activities are focused on the development of methodologies to assess health effects from the exposure to chemicals and their mixtures (biomarkers of exposure and effects). Major problems in evaluating co-exposure of consumers to chemical mixtures were presented at the ISEA 2003 Satellite "Workshop on Cocktail Effects", which was jointly organized by the JRC and the EEA (European Environmental Agency). A toxicogenomic approach was developed to identify early markers of effects during development by long-term exposure of low doses of laboratory animals to chemicals and analyzing the gene expression in target organs and tissues. These studies will be extended to co-exposure to mixtures of chemicals at environmental doses from foetal period to adult age. Gender difference represents a major example of gene-environment interactions, as it was demonstrated by our studies on the semi-chronic exposure to arsenic in drinking water.

The relevance of individual gene patterns in modulating the toxic responses following exposure to chemicals was a major conclusion at the Workshop on "Gender Difference in Risk Assessment" jointly organized by the JRC and SGOMSEC (exact name) in November 2003. The use of DNA-macroarrays technologies for diagnostic purposes was explored by analyzing the gene expression in a human kidney cancer specimen. A joint activity with the European Organization for the Research and Treatment of Cancer has been initiated to characterize the gene expression pattern in kidney cancer in 40 case study specimens from several European Countries.

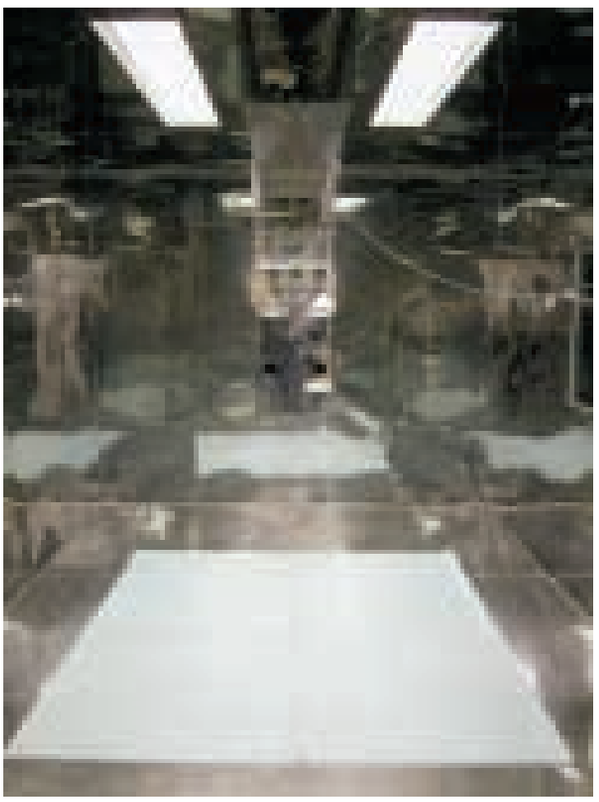
The INDEX project (Critical Appraisal of the Setting and Implementation of Indoor Exposure Limits in the EU)

The main purpose of the project is to provide a prioritized list of indoor originated chemical pollutants that could be regulated in the future. This list will be formed based on the risk assessment, which will be done by combining existing exposure data of the European populations and the available toxicological doe/response data. Finally, the project will provide suggestions and recommendations on potential exposure limits for the prioritized substances. In 2003 a list of indoor pollutants, including benzene, formaldehyde, acetaldehyde, CO and NO_2 has been established, to be considered of high priority for future regulatory actions. Risk assessment reports for these compounds are partly prepared and discussed. This work will continue and will be finalized by December of 2004.

Photo-catalytic Innovative Coverings Applications for De-pollution Assessment (PICADA)

A European consortium of industrial enterprises, research institutions and the JRC is running a test programme for innovative construction materials set to help in the fight against air pollution. The "smart" construction materials (plaster, mortar, architectural concrete) and coatings are developed in the frame of the PICADA project.

The results of the studies undertaken (in the INDOORTRON facility) lead to the conclusion that construction materials and coatings containing titanium dioxide (TiO_2) play a significant role in the degradation of organic and inorganic air pollutants after illumination with UV and/or solar radiation. After six hours of irradiation it was calculated that up to 30% of NO_2 and up to 90% of NO were photo-catalytically degraded. For NO_2 more ad-/absorption phenomena were observed than for NO. As far as the photo-catalytic velocity is concerned, a value of 0.2 cm/sec was calculated for NO_2 and 0.3 cm/sec for NO, after 1 hour of irradiation.



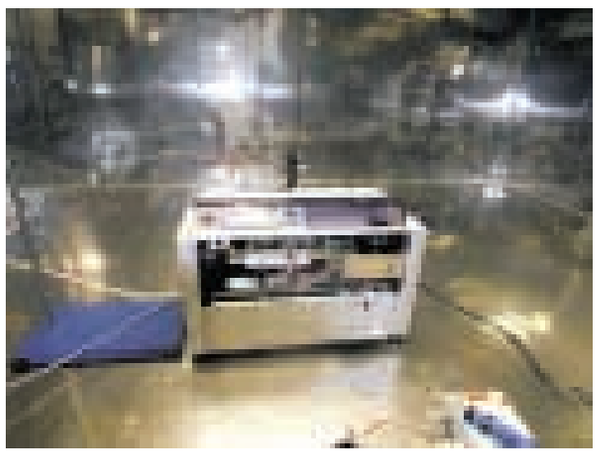
The INDOORTRON with titanium dioxide coated construction material

Preliminary Results on the Impact of Various Air Exchange Rates on the Levels of Environmental Tobacco Smoke (ETS) Components

In the frame of activities to evaluate human exposure to ETS components in indoor environments, a series of tests were undertaken in 2003 to investigate the impact of various ventilation rates on the air concentration of ETS-components. The tests were carried out at the European Commission-Joint Research Centre's INDOORTRON facility, a 30 m^3 walk-in type environmental chamber.

Preliminary evidence indicates that changes in ventilation rates simulating conditions expected in many residential and commercial environments during smoking do not have a significant influence on the air concentration levels of ETS constituents, e.g. CO, NO_x, aromatic compounds, nicotine. This suggests that efforts to reduce ETS originated indoor air pollution through higher ventilation rates in buildings, including residential areas and hospitality venues, would not lead to a meaningful improvement of indoor air quality.

Moreover, the results show that "wind tunnel"-like rates or other high rates of dilution ventilation would be expected to be required to achieve pollutant levels close to ambient air limit values.



The smoking machine installed inside the INDOORTRON

European Collaborative Action (ECA): Urban Air, Indoor Environment and Human Exposure

In 2003, the European Collaborative Action on "Urban Air, Indoor Environment and Human Exposure" issued the Report No. 23 on "Ventilation, good Indoor Air Quality and rational use of energy".

The aim of this report is to provide information and advice to policy and decision makers, researchers, architects, designers, and manufacturers on strategies for achieving a good balance between good indoor air quality (IAQ) and the rational use of energy in buildings, available guidelines and assessment techniques on energy and IAQ, significant trends for the future with implications for IAQ and the use of energy in buildings; and an indication of current research issues.

ACTION THEXAS PHYS

In the frame of a holistic approach to the total human exposure concept, the health effect of physical stressors, like UV radiation, noise and EMF on human well being will be estimated and assessed as the basis for the development and implementation of common measurement methods and protocols — common exposure models and exposure guidelines.

The work will be carried out in dedicated laboratories specialised in the different types of exposure pathways and stressors. These are being developed to act in their

respective areas as Reference Laboratories at EU level to improve the currently achievable quality, representativeness and comparability of measured data related to consumer and occupational exposure.

The following activities were carried out in 2003:

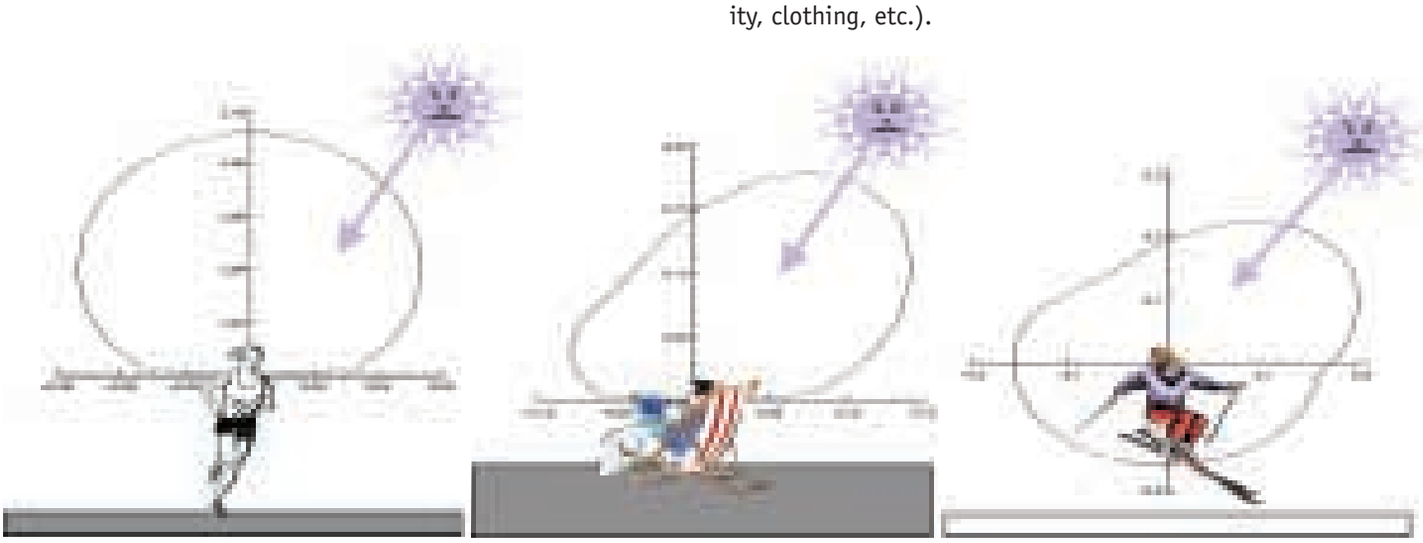
UV Radiation measurements of the European Reference Centre for UV Radiation Measurements (ECUV)

The PCE Unit hosts the European Reference Centre for UV Radiation Measurements (ECUV, **http://ecuv.jrc.it/**). The main task of ECUV is to support the quality assurance of spectral solar UV measurements in Europe. It also continuously monitors the solar UV radiation at the JRC Ispra site. A mobile spectroradiometer system has been developed and validated. The advantages of this approach are that local monitoring instruments do not need to be transported and are used in their natural environment during the intercomparison. Furthermore, a site can be visited at regular intervals to check its stability over extended time periods. While this is a more realistic evaluation of a monitoring site, it places strict criteria on the performance and operation of the mobile instrument that must be proven to be stable at a level against which all other instruments will be judged. The quality assurance of spectrally resolved ultraviolet irradiance measurements was performed at 14 UV monitoring sites in Europe using a mobile spectroradiometer system developed within the project QASUME (Quality Assurance of Spectral Ultraviolet Measurements in Europe through the development of a transportable Unit) The results obtained so far have confirmed the unique potential offered by such a mobile unit for providing on-site quality assurance of solar ultraviolet irradiance measurements.

Satellite-derived UV climatology and UV Human Exposure Modelling

The first version of a European satellite-derived UV radiation climatology over Europe was completed in 2003. It covers the period from January 1984 to October 2003. It consists in maps of the surface dose rates and daily doses, covering Europe (12E-32E, 34N-74N) with a spatial resolution of 0.05 deg. The method basically consists in using a standard radiative transfer code (UVspec) and in exploiting various sources of information to assign values to the influencing parameters. GOME, TOMS or TOVS data are used for the total column ozone. The maps are available for several action spectra: UVA, UVB, erythemal, SCUPh (Skin Cancer), DNA and PLANT. The data set documents the year-to-year variability in the UV radiation during the 19 years period, which varies according to the month and can reach ±50% over large areas.

In a subsequent step these data are used for human exposure modelling. The UV exposure of a person strongly depends on behaviour (activity, clothing and protection measures, location in space and time). The different parts of the body also receive very different doses, depending in particular on the orientation of the skin surface (e.g. the exposure of the face is closer to that of a vertical surface, that of the shoulders to an horizontal surface). So far, the UV climatology contains the so called “downwelling irradiance”, which represents the exposure of a horizontal surface. The intermediate outputs of the climatology and the radiative transfer models allow estimating the directional distribution of the surface UV light (radiance) and hence the exposure of an arbitrarily oriented surface. In this way, the potential exposure can be computed for different parts of the body. To approach the real exposure it will still be necessary to take into account the other factors (activity, clothing, etc.).



Cloudy sky, low UV surface albedo **Clear sky, low UV surface albedo** **Clear sky, high UV surface albedo**

Scheme on different exposure situations

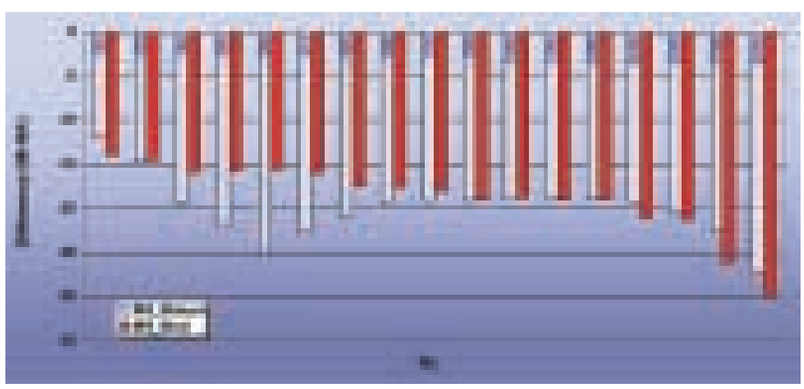
JRC-Noise Laboratory
Formulation and implementation of directives related to environmental noise

In 2003, the PCE Unit has established the Environmental Noise Monitoring Lab (ENML), which consists of three mobile units for long-term noise and micrometeorological measurements. The ENML supports the development and validation of harmonized noise computational and measurement methods in the EU and is involved in several projects with the aim to study personal exposure to environmental noise and associated health effects, including research concerning the interaction among physical and chemical stressors and their potential health effects.

In the context of the HARMONOISE project ("Harmonised, Accurate and Reliable Methods for the EU Directive on the Assessment and Management of Environmental Noise") five measurement campaigns to collect noise & micrometeorological data, needed for the validation of the harmonised models under development, were prepared and successfully performed in (7-15 April 2003, La Crau (F), 30 June to 8 July, 2003, St. Berthevin (F), 21-31 July 2003, Vada (I), 29 September to 8 October 2003, St. Berthevin (F) and 20-31 October 2003, Vada(I)).

The analysis of the data measured in the first experimental campaign of the HARMONOISE project showed some typical behaviour of sound propagation and some interesting results: at distances from the source higher than 300 m, the attenuation of noise is almost the same at all frequencies (unlike at shorter distances in which the attenuation at high frequencies is normally higher than the one at low frequencies), considering the characteristics of the terrain, and for certain meteorological conditions (absence of wind, etc). The comparison between the measurements and the predictions of the theoretical model showed generally good results, but the model seems not to take into account the presence of a hollow at 250-315 Hz (Fig. 1). The aforementioned discrepancies show that results the of the HARMONOISE Project will be very important to improve the performance of existing prediction models, taking into account meteorological conditions, above all at long distances.

Under request of different noise stakeholders in the EU the JRC-IHCP/PCE/ENML undertook the initiative to standardise at European level the methodologies to measure acoustic ground impedance, a parameter which largely influences outdoor noise propagation. A technical meeting was organised to make a first comparison among the different techniques (27-29 October 2003, Vada (Tuscany).



Comparison between Measurements and PROPLIN Model:
M1 vs M9 GradT=0, No Turbulence

European Information System on Electromagnetic Fields (EIS-EMF)

The main objective of EIS-EMF, is to implement a EU-wide programme on EMF risk communication, and contribute to the development of a EU Official risk communication channel on EMF. The aim is to **(1)** provide quality information and advice for the EC and MS actions and communication needs, and **(2)** promote common practices and standards for risk perception monitoring and risk communication at EU level, and elaborate tools for the dissemination of information to stakeholders and EU citizens. In 2003 the development of a Web-based information platform on public health issues related to EMF has commenced. In addition, a forum for a systematic stakeholders dialogue between scientists, industry, NGOs, and EU policy-makers, is currently being set up together with a FP6 EU-wide Scientific Network (EMF-Net) to identify, analyze, validate and disseminate information on emerging issues related to human exposure to EMF.

Action 4315: BEVABS

For several years BEVABS has contributed to the development of advanced analytical methods based on Nuclear Magnetic Resonance (NMR) and Isotopic Ratio Mass Spectrometry. These methods have a broad potential of application for many aspects of European policy. The institutional work for the EU Wine Isotopic Databank is carried out in close collaboration with official Member States laboratories (EC Reg 2729/2000). In

the past years, BEVABS has carried out the development and validation of the method for the determination of the $^{13}C/^{12}C$ isotope ratio of ethanol, which has been adopted at International level by the Office International for Wine and Vine (OIV) and in March 2003 as official method by the European Union (EC Reg 440/ 2003). A workshop was organised in June 2003 with the specific objective of extending the network of EU Wine Databank official laboratories to Candidate Countries and to establish the state of the art of NMR and isotopic techniques applied to anti-fraud in Europe. BEVABS continued transferring know-how through continuation of specific training of scientific staff from Member states and accessing countries: 1expert from Portugal, 1 from Austria and 2 from Czech Republic stayed in BEVABS laboratory for periods of 2 to 3 weeks for specific training on isotopic analysis of wine and other goods. Three rounds of FIT-Proficiency testing (Food analysis using Isotopic Techniques network- Proficiency Testing) were organised in 2003 and were used for monitoring the performance of isotopic measurements within the network of laboratories of the EU Wine Databank. Besides, very active research has taken place through shared cost actions projects, for development of new methods for detection of fraud, control of authenticity and verification of the origin of goods and agricultural products. The projects MEDEO (NMR and isotopic techniques for detection of adulteration of olive oil) and GLYCEROL (methods for detection of adulteration of wine by illicit addition of glycerol) were completed in 2003 and the main results will be communicated to interested bodies (DG AGRI, International office for Wine and Vine and International Oil Council). Three projects will be continued in the next years: WINE-DB (extension of EU Wine Data bank to several Candidate Countries and non EU countries), SPREADS, (detection of adulteration of spreadable fats), COFAWS (confirmation of the origin of farmed and wild salmon).

A considerable part of the above projects are dedicated to NMR profiling techniques and are now extended to metabolite fingerprinting and identification of biomarkers in biological matrices (Metabonomics) in link with the actions THEXAS-PHYS and THEXAS- CHEM. This approach is foreseen to be further developed in the next years in relation to the Environment and Health and human exposure issues.

A scientific highlight of 2003 was the second International Symposium on Isotopomers (ISI 2003, Stresa on 4-6 November). The symposium was organized by IHCP with the collaboration of IES and the support of Japan Science and Technology Agency and of the International Atomic Energy Agency. High level scientists from EU Member Sates, Norway, US, India and Japan participated in ISI2003 for presentation of research works on isotopomers ranging from Environmental studies to analytical methods for food authenticity or for medical diagnostics (**http://ihcp.jrc.cec.eu.int/EVENTS/ISI2003/isi2003.html**).

The NMR laboratory of BEVABS

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bms

Biomedical Materials and Systems

Institutional Actions
Nanobiotechnology for Health Applications (NBT)

Competitive Projects
STERIPLAS, BIOGRAD, IFCA, LAPLADIS, MEDPHOT, EVIGeM, SPOTS, "COMO", PLASMATECH

Web information resources
http://ihcp.jrc.it
http://bms.jrc.it
http://ihcp.jrc.cec.eu.int

In the last five years, the BMS-Unit has developed as a horizontal "enabling" technology provider in support of the JRC priority areas for policy related research. The Unit's strength lies in the cross-functional research activities, which are performed in the frame of two institutional Actions on 'Nanobiotechnology for Health Applications' (NBT) and 'Medical Devices and Health Technology' (MEDTECH), which were initiated in FP6.

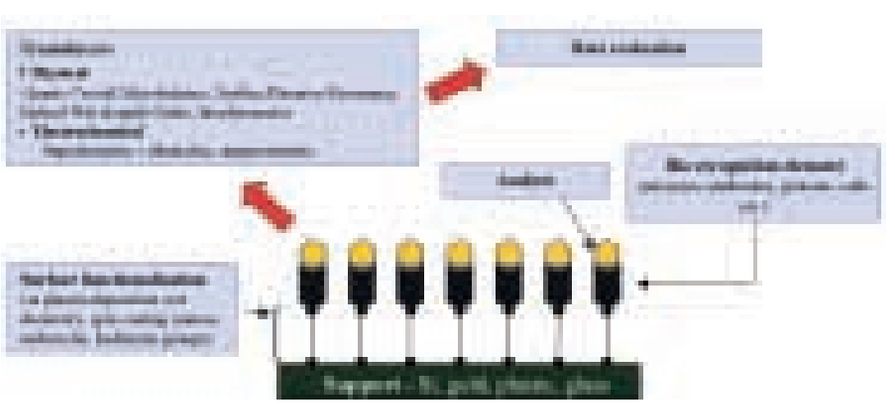
NANO-BIOTECHNOLOGY FOR HEALTH APPLICATIONS

At the convergence of physics, chemistry and biology, *Nanobiotechnology* deals with the understanding and transformation of biosystems (living or non-living) to create and use functional structures, devices and systems, which have novel properties and functions that are associated with their small and/or intermediate size. This allows, for instance, to study biological systems at a scale not attained before, to modify interfaces in order to improve their compatibility with biological entities, and to create new probes or sensors with unique, size-specific properties on the atomic or molecular length scale. These new opportunities are of major importance for the development of high throughput screening systems for toxicology applications as well as for chip technologies. Miniaturisation down to the nanometer scale will be one of the great challenges within the next years.

The NanoBiotech IHCP institutional project aims at building a technology platform based on long range experience in surface engineering and opto-electronic devices that will allow us to develop new bio-interfaces, biosensors and diagnostics systems with applications in the emerging Environment and Health priority. Applications in the field of chemicals toxicology testing and chemical exposure are evaluated through the collaboration with other Units of the JRC (ECVAM and PCE). The objective to integrate the Nanobiotech project into the European Research Area (ERA) has been particularly successful with our participation in the Network of Excellence Nano2Life. This is the first European network on Nanobiotechnology where IHCP-BMS has a central role in defining the joint research programme of the Network.

A biosensor is generally defined as a compact analytical device incorporating a biological or biologically derived sensing element either integrated within or intimately associated with a physicochemical transducer. A biosensor produces either discrete or continuous signals, which are proportional to the concentration of a single analyte or a related group of analytes. The interaction between the analyte and recognition biomolecules is an event on the molecular scale, which can be detected as a local change in mass, in optical or electrical properties. Recognizing elements are generally biomolecules such as enzymes, antibodies or even cells with highly specific recognition abilities, which are usually immobilized on solid supports. Such transducers can be devices such as piezoelectric materials, electrodes or wave-guides that are based on the analyte-biomolecule interaction and yield a measurable electric or optical signal of their corresponding response.

The NBT activities are focused on two essential subjects of research, the biological/non biological interfaces as well as related end point detection methods.



Classical biosensor architecture

Interfaces

The interaction between the organic recognition biomolecule and inorganic transducer surface is a key aspect in the development of a biosensor, since it has a direct consequence on the sensitivity and the specificity of sensing. In order to guarantee high sensing performance, engineered surfaces must be developed for the immobilisation of the recognition biomolecules that can interact specifically with the target molecules such as proteins, enzymes or antibodies. In particular, new surface coatings must be assessed with regard to their physical and chemical stability and their protein adsorption capacity.

Patterning of these surfaces at the sub micron level is an additional essential step to match the sensor performance to the requirements and to develop miniaturized sensitive, fast, portable and multi analysis sensors.

The physical and chemical properties as well as the microstructure of the functionalised surfaces, interfaces and layers are characterised with advanced techniques as Atomic / Chemical Force Microscopy (AFM/CFM), X-ray Photon-Electron Spectroscopy (XPS), Time-of-flight Secondary Mass Spectroscopy (ToF-SIMS), Scanning Electron Microscopy (SEM), Quartz-Crystal-Microbalance with Dissipation Analysis (QCM-D), etc.

Surface functionalisation

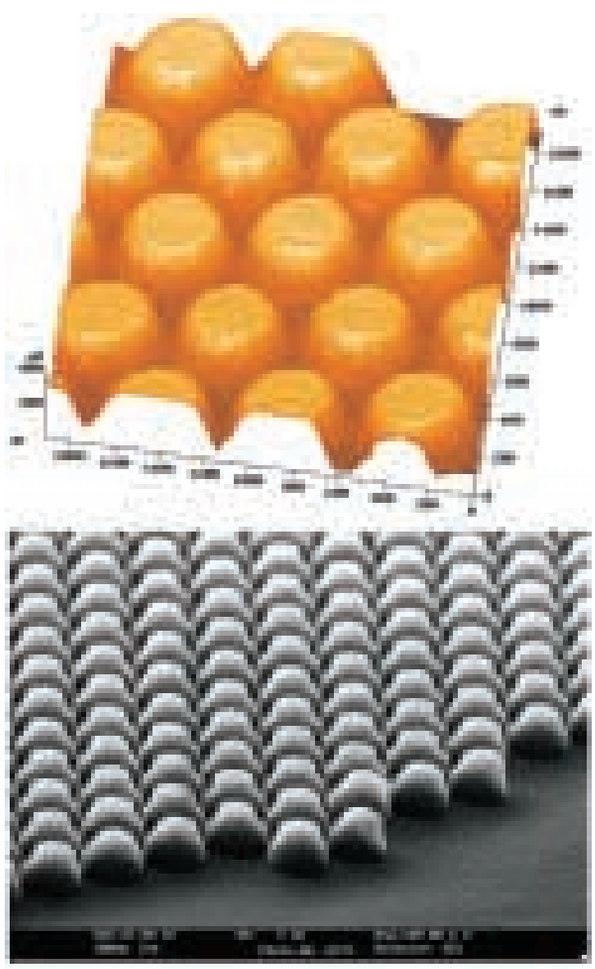
The activities in 2003 were concentrated on the synthesis of surfaces with different physical and chemical functionalities for triggering the interactions between the bio-molecules and the transducer materials. Polymeric films with different properties i.e. protein adsorbing (fouling) and protein resistant (anti-fouling) were synthesised via Plasma Enhanced Chemical Vapour Deposition (PE-CVD). Functional surfaces with $-NH_2$ or –COOH functional groups promoting controlled protein adsorption have been produced by poly allylamine (pAL) and poly acrylic acid (pAA) film deposition, respectively. Protein resistant films have been developed by deposition of poly-ethylene glycol (PEG)-like films. The efficiency of the developed layers with regard to protein adsorption has been verified with QCM-D. This technique allows studying the formation of thin films such as proteins, polymers and cells on surfaces in a liquid by measuring both the dissipation and the resonance frequency of a quartz crystal. The stability of pAA- and PEG like films upon addition of phosphate buffered solution (PBS) has been verified. A high level of Bovine Serum Albumin (BSA) adsorption on pAA films (0.3 $\mu g/cm^2$) has been observed as compared to anti-fouling film (PEG).

Another important category of materials in the area of biochemical sensors are those based on electrochemically grown conductive organic polymers such as polypyrrole (PP) and polyaniline. The usefulness of these materials derives from the relative simplicity by which they may be deposited together with enzymes or antibodies such that the active biomolecules become physically trapped or immobilized in a conductive matrix without suffering excessive denaturing. This conductive matrix with a biochemically active component may then be used as transducer in sensors based on electrochemical or impedometric detection methods.

The preliminary studies conducted in this area have concentrated on the development of porous silicon as a high surface area substrate for deposition of galvanostatically deposited polypyrrole (PP). Conditions have been determined which produce stable uniform relatively smooth polymer films, which have been characterization using surface analytical techniques such as XPS and TOF-SIMS. Detailed surface mass spectrometry studies of PP and deuterium substituted PP have been undertaken and will provide the basis for future detailed studies of the polymer system when biomolecular species will be incorporated in the conductive film matrix.

Functionalised surface nano-patterning

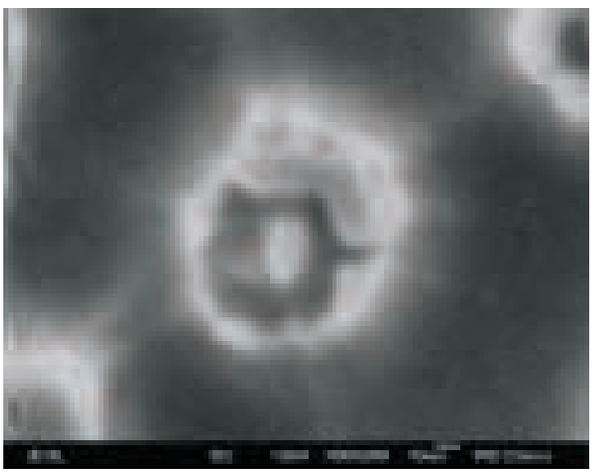
For improving the sensor sensitivity, e.g. to decrease harmful background signals, nanostructured surfaces are produced for local control of the protein adsorption. Using nanosphere lithography, nano-domes with COOH functionalities distributed on a substrate having anti-fouling properties were produced generating a chemical contrast on a single surface at the sub-micron level. The process has been carried out combining plasma deposition and etching techniques with colloidal particles masking. The picture below shows an example where polymeric nano-domes of about 50 nm width have been created at the top with bio-specific chemical functionalities.



Atomic Force Microscopy and Scanning Electron Microscopy images of the nano-structured surface

Surface - Protein interaction

Protein adsorption experiments using Bovine Serum Albumin (BSA) as a model protein, were performed on the 'nano-dome' surfaces. A Field Emission-Scanning Electron Microscope (FESEM) was used for the topographic characterisation of the adsorbed proteins. The results evidence how the small BSA clusters (10-30 nm) are selectively bonded to the functional plateau of the pAA-domes. In particular they arrange themselves in the centre of the plateaus and on the edges where the surface free-energy is very high. No BSA was found in the surrounding matrix. With this method, a controlled organisation of protein films can be obtained.



BSA protein selectively bond on domes top surface

END POINT DETECTION

The development of biosensors with potential applications in the field of chemical exposure is another objective of the Nanobiotech project. Chemical exposure biosensors are produced using the Quartz Crystal Microbalance technique and the Surface Plasma Resonance (SPR) method.

Sensors based on antibody-antigen interactions

In 2003 a biosensor has been developed, which is based on antibody-antigen interactions to detect a particular environmental or food contaminant. The covalent antibody binding on the quartz crystal gold surface is achieved on amine functionalised surface through the deposition of a Self-Assembled Monolayer (SAMs) using 4-aminothiophenol. The antibody binding is performed using glutaraldehyde for cross-linking and protein A for better antibody orientation. SAM or polymer formation stability studies in phosphate buffer solution (PBS) are performed using QCM-D. After the optimisation of each step, antibody-antigen interactions will be monitored using the QCM-D for detecting Ab-Ag binding.

Fluorescence Techniques

The Nanobiotech project is also providing direct scientific and technical support to the ECVAM Unit in the area of endpoint detection. End point measurement is a key step in the toxicology testing of chemical substances using in vitro cell-based assays. Responding to the significant demand for more rapid and more sophisticated test methods, with the adoption of the new EU chemicals legislation, the Nanobiotech project aims to assist ECVAM in applying advanced optical measurement techniques to improve the efficiency, reliability and specificity of regulatory toxicity tests which use cells and engineered tissues in culture.

Among the techniques being investigated, fluorescence based methods are of particular interest. However, unlike traditional fluorescence labelling approaches that rely on the addition of a fluorescence stain or dye, our methods are primarily based on identifying and measuring the concentration of endogenous fluorophores, which are already present in the cell or medium. Although it is more technically challenging to detect the very low levels of fluorescence light emitted by small concentrations of endogenous fluorophores (also known as auto-fluorescence), it allows a completely non-destructive analysis of an assay and eliminates many chemical processing steps associated with endpoint detection that are often time consuming and prone to operator error. One innovative feature of the auto-fluorescence imaging system being developed for ECVAM is the inclusion of an acousto-optic tuneable filter (AOTF). This device, when mounted on a viewing port of a fluorescence microscope, offers an exceptional extinction ratio resulting in almost complete elimination of background noise. The ultra-high signal-to-noise performance, coupled with the possibility of randomly accessing an infinite amount of different filtering wavelength bands, has led to the development of a powerful fluorescence imaging spectrometer capable of detecting and mapping fluorescent biomolecules. In parallel with the construction and optimisation of the detection system, work is underway in identifying candidate endogenous fluorophores which concentration is directly linked to a toxicological endpoint. For example, acute toxicology assays often aim to assess cell viability through an endpoint measurement that indicates the level of mitochondrial activity. NAD(P)H is an endogenous fluorescent molecule that is inherently involved in the metabolic process in cells and thus if monitored, can report on the viability of the cell without the addition of exogenous substances.

Another fluorescence technique being applied to in vitro toxicology testing is fluorescence lifetime measurement (FLM). Rather than considering only the spectral characteristics of fluorescent molecules, this method actually measures the decay time or lifetime of fluores-

cence emission stimulated by a very short pulse of excitation light. In our set-up we employ a picosecond pulsed violet laser diode (405nm) to excite the sample and a Time Correlated Single Photon Counting system to detect the time of arrival of each emitted fluorescence photon. With suitable digital signal processing of the acquired data a specific decay time can be calculated for a particular fluorescent wavelength. Since different fluorophores that emit at the same wavelength can be distinguished by their decay times, this method offers the possibility of detecting particular fluorescent biomolecules in the presence of significant autofluorescence background generated by other fluorescent biomolecules. Current efforts are focusing on integration of the FLM system on a fluorescence microscope to allow fluorescence lifetime imaging (FLIM) of cell-based toxicology assays.

Cyclotron Applications

In 2003, the general overhauling of the cyclotron was concluded. The scientific activities were concentrated on production technologies for medical radioisotopes and materials research. Special emphasis was given to training activities of young researchers including external funding through the Marie-Curie Programme (Joint ECVAM-BMS MC-Training Site, individual MC fellowships).

MEDICAL RADIOISOTOPES

Fluorine-18 production

On December 19th, 2003 a contract has been signed between Amersham Health (now: General Electric (GE) Healthcare) and the JRC Institute for Health and Consumer Protection to begin at the Ispra Cyclotron the commercial production for radiotracers for cancer diagnosis. The collaboration started in October 2001 with the scope to establish at the Ispra Cyclotron a radiopharmaceutical production site for short-lived fluorine-18 (18F) labelled radiotracers for Positron Emission Tomography (PET). This resulted in the set-up of a production according to the latest standards Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) as well as with licensing procedures for short-lived radiopharmaceuticals.

Hot cell for the production of the radiopharmaceutical 18F-FluoDeoxyGlucose

The Ispra Cyclotron hosts the first production facility in Italy with the license to sell 18F-FDG (18F-FluoDeoxyGlucose) on the market. Up to now the wide use of this technology was hampered by the high investments required to establish a cyclotron centre together with a PET facility. The example will trigger more such licensing procedures all over Italy and improve the access of patients to PET diagnostics while making more economic use of cyclotron capacity. This will improve appreciably the access of cancer patients in Italy to Positron Emission Tomography.

Radioisotopes for Therapy

Radiolabelled tumour seeking molecules have received increased attention in the last decade, since they offer significant advantages over traditional therapy approaches:

- Radiation doses for killing tumour cells can be delivered with tiny chemical quantities avoiding the side effects of chemotherapy.
- The particle radiation can kill also tumour cells with no immediate up-take of radiopharmaceuticals. This “cross fire effect” is a major advantage over genetic approaches to cure cancer.
- The variety of radioisotopes allows adjusting dose rate and the striking distance of the “isotope cocktail” to the volume of the cancer to be treated.
- With the proper carrier molecules and a good matching biological and physical half-life of the radiopharmaceutical this internal radiotherapy allows the treatment of already disseminated cancers.

For these reasons the IHCP participates in research efforts to make available the most promising cyclotron produced radioisotopes like alpha-emitters (e.g., 211At) and beta-emitters (e.g., 64Cu). These activities have to be pursued with increasing intensity since the number of cyclotron facilities capable of producing nearly every desired radioisotope is shrinking within in the EU. The IHCP follows these activities in close collaboration with external partners that guide the efforts towards most promising radioisotopes. The IHCP efforts are now co-ordinated with those of JRC-ITU, which has a strong involvement in alpha immunotherapy trials, both clinical and pre-clinical.

Support to Technological Development in Radiotherapy

The cyclotron is also supporting new approaches in radiotherapy using particle beams. This new field of hadron therapy (in Europe developed mainly at the GSI Darmstadt in Germany), uses ions like protons, alpha particles, carbon ions or even heavier particles. By adjusting the energy of the ion beam the depth of the main energy deposition can be adjusted to the requirements of tumour irradiation with low radiation delivered to healthy tissue.

In collaboration with the TERA (**TErapia con Radiazioni Adroniche,** Therapy with Hadronic Radiations) Foundation support is given to the development of hadron therapy by providing particle beams for the testing and development of equipment to monitor the beam intensity profile online during irradiation. Such equipment is essential for treatment planning, medical quality control and patient safety.

New detector for beam intensity profiles in hadron therapy

BIOMEDICAL MATERIALS - TRAINING ACTIVITIES

Between 10% and 30% of the patients, who have received a joint prosthesis relying on a metal-polyethylene (UHMWPE) articulation, require a revision surgery already after approximately 10 years due to aseptic loosening of the implant. There is strong evidence that this loosening is caused by the accumulation of submicron sized wear debris in the periprosthetic tissue. Thus, the main goal of research in improving the durability of orthopaedic implants is to reduce the number of wear debris released from the implants.

The IHCP Orthopaedics Implant Testing Laboratory has focused its activities in 2003 on wear and release test methodologies using nuclear techniques. In this way the added value of the IHCP cyclotron to these activities could be increased. Together with ECVAM the BMS Unit hosts the Marie Curie Training Site BIORAD which provides training to doctoral fellows on toxicity test methods for biomaterials, particularly metal toxicity.

In the frame of the FP5 Shared Cost Action "BIOGRAD" screening wear tests a new methodology for screening wear tests of ceramic-ceramic wear couples based on the ASTM 732 Reciprocating-Pin-Flat Test has been successfully demonstrated.

Clinical and experimental studies indicate that modular hip joint prosthesis, artificial knee joints and spinal fixators are prone to fretting corrosion damage indicating a clear need for research. An exploratory research project, supported through an individual Marie Curie Fellowship, has initiated in 2002, with the aim to develop a quantitative and precise methodology for fretting corrosion studies by combining radiotracer techniques with mechanical testing. It has been demonstrated that material releases in the order of μg can be detected, which is beyond the resolution of gravimetric methods. By element-specific charged particle activation the release of certain ion species can be monitored online during fretting fatigue in liquid media. First studies have been conducted in 2003 to simulate the ion release from the spherical head and the stem.

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RUSET, C.*, GRIGORE, E.*, COLLINS, G.*, SHORT, K.*, ROSSI, F., GIBSON, P.N., DONG, H.*, BELL, T.* "Characteristics of the Ti_2N Layer Produced by an Ion Assisted Deposition Method". *Surface and Coatings Technology,* Vols. 174-175 (2003) 698-703, Elsevier - ART 91115

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WACK, S.*, HAJRI, A.*, HEISEL, F.*, SOWINSKA, M.*, BERGER, C.*, WHELAN, M.P., MARESCAUX, J.*, APRAHAMIAN, M.* "Feasibility, Sensitivity and Reliability of Laser-Induced Fluorescence Imaging of Green Fluorescent Protein-Expressing Tumors *in vivo". Molecular Therapy,* Vol. 7, No. 6 (2003) 765-773 - ART 91540

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Contributing to the European Research Area

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

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

NETWORKS

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

- European Network of GMO Laboratories (ENGL)
- European thematic network on Optical Methods for Medical Diagnosis and Monitoring of Diseases (MEDPHOT)
- European thematic network on Innovative Plasma Technology for Societal Needs (PLASMATECH).

ECVAM collaborates in 15 Networks in the form of Task Forces on Acute fish toxicity, Biocompatibility testing, Blood-brain barrier, Carcinogenicity, Endocrine Disrupters, Good Cell Culture Practice, High-throughput screening, Metabolism, Neurotoxicity, Pyrogenicity, (Q)SARs, Sensitisation, Shellfish toxin testing, Skin Irritation and Toxicogenomics. Moreover, 1 Steering Group on Biologicals was established with 6 members from 6 countries. In total, 99 members from 14 countries (distribution: 35% Italy; 16% UK; 13% Germany; 11% France; 8% The Netherlands; 13% Others) are collaborating and disseminating information on tightly defined tasks.

FACILITIES

The IHCP has a combination of facilities that have to be set up at the EU level. Some of these facilities are:

Biocyclotron
The Biocyclotron is a highly versatile particle accelerator with a rather large energy range and the capability of accelerating protons and alpha particles (up to energies of 40MeV) as well as deuterons (up to 20MeV). With this facility a wide variety of radioisotopes can be produced, making it especially suitable for research purposes.

Indoortron
The Indoortron laboratory is a unique, 30m^3 volume walk-in environmental chamber featuring controlled temperature, relative humidity, air quality, and air exchange rate.

BEVABS
BEVABS has a specialized laboratory that aims to ensure correct implementation of EU wine quality legislation.

RESEARCH TRAINING AND MOBILITY

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

SUPPORT TO EU ENLARGEMENT

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

- ECVAM organised a practical training course on in vitro methods for pyrogenicity testing in Hungary and a workshop on alternatives to the use of animals in higher education in Poland.
- Two PhD students from Candidate Countries are currently working at ECVAM on the development of structure-activity relationships for pharmacotoxicological endpoints and on the development of in vitro testing methods for assessment of neurotoxic and neurodegenerative potential.
- A scientist from Poland worked at ECVAM for a period of six months in the key areas Systemic Toxicity and Strategic Developments.
- During 2003, the JRC continued to host a doctoral fellow from Bulgaria, to carry out a PhD on the QSAR modelling of regulatory endpoints, in collaboration with Liverpool John Moores University (UK).
- In support to the EU enlargement, a IUCLID course was given in October 2003 in Bratislava (Slovakia). The course was highly appreciated by the participants from the competent authorities in the new Member States. More courses are scheduled in 2004. In order to facilitate the correct use of IUCLID 4.0, Guidance Documents are being drafted in the frame of a joint collaboration with CEFIC.

E-training tools within the JRC enlargement action on GMO detection

In order to reinforce Enlargement Action and respond to the continuously increasing need of training beyond the available training capacity, a new strategy based on the use of multimedia tools for training was proposed and introduced. The aim is to increase efficiency, productivity and availability of training efforts by complementing traditional training courses with new tools, such as interactive DVD training. This activity is still ongoing and the release is expected in 2004.

Finally, during 2003 three DNE/VS from Romania, Czech Republic, and Poland were hosted and trained for a total period of 10 months. During this period, specific individual work programmes were followed to respond to individual specific needs in the field of GMO detection, and to allow direct participation in ongoing research activities.

IHCP Performance Indicators–2003

Prizes/Awards

- Thomas Hartung was granted a honorary professorship at the University Konstanz, Germany and the Award for Environment and Society by LBS Baden-Württemberg, Germany.

Nominations

- The US Environmental Protection Agency (EPA) has nominated Andrew Worth as an expert consultant in a newly-established Panel of the EPA Scientific Advisory Board on Computational Toxicology.

Patents (received by IHCP)

- EP patent application on "Functionalization of intracoronary stents" (EP n° 02292525.9)

Training

- **International training courses: analysis of food samples for the presence of GMOs.** The activity started in the year 2000 as part of the collaboration between JRC and WHO to promote food safety related issues in WHO European Region, inside and beyond current EU borders, with special consideration for Accession Countries, as well as Central and Eastern Countries with transitional economies. The experience was very positive followed by intense contacts with the participants, who frequently requested our advice for the implementation and/or optimisation of laboratories devoted to the analyses for GMO detection. A second series of three Training Courses was organized in the years 2002-2003, with extensive participation of candidates from Accession Countries.

  To enlarge and enhance the benefits of training and to support local training initiatives, the B&GMO Unit explored the possibility to act as Training Centre for trainees. For this purpose, one scientist from the Agricultural Biotechnology Centre (Environmental Biosafety Research Institute - Gödöllõ, Hungary) was hosted for 2 months in the B&GMO facilities. As a successful follow up of this initiative a Training Course, specifically directed to Accession Counties, took place in Gödöllõ, in November 2003.

  Additionally, a training manual as a permanent source of information describing all the techniques currently used for the detection and quantification of GMOs was produced, edited and published in 2003 (**http://gmotraining.jrc.it/**). The manual covers a wide variety of techniques for GMO detection, identification, characterisation, and quantification, including theoretical information crucial for anyone wishing to enter the field of GMO detection. The manual, which is the first one published on this topic, is currently being translated into Turkish and Russian for further publication.

- In 2003 the **ECB** organized 2 training courses regarding IUCLID and the EU risk assessment procedures and 3 IUCLID courses were successfully given to authorities of the member states, candidate countries and industry within ECB's activities on biocides.

- **BEVABS** provides training for new users of isotopic techniques, organises proficiency testing, communicates technical recommendations and supports accession countries in joining the operational network of EU wine databank anti-fraud laboratories.

- The **BIORAD** Marie Curie Training Site (ECVAM and BMS Biocylotron laboratories) aims at high-level interdisciplinary doctoral training on biomaterials testing using radiotracers.

B&GMOs

GM-FOOD & FEED

Aim:

Aim: Proposal for complementing the envisaged action in the JRC work programme on GMOs to conduct further work on post-market monitoring of GM food and feed, to develop further guidance on detection and sampling of GM food and feed, to provide scientific support to the Commission's participation in international negotiations, notably in Codex Alimentarius, and to organise a stakeholders' conference (forum) on GMOs in 2003.

ECB

ECICS

Aim:

The purpose of this work is to carry out a study to assess the feasibility of updating ECICS. This work will be used to support DG TAXUD plans for updating and improving ECICS over the next two years.

OMNITOX

Aim:

The main activity is to conduct a feasibility study on the potential for applying (elements of) Life Cycle Assessment (LCA) in chemicals policy.

Partners:

- Chalmers University of Technology AB (S); AB Volvo Technological Development (VOLTD) (S); Procter & Gamble Eurocor NV (PGEUR) (B); Stora Enso Oyj (FIN); Antonio Puig SA (E); Randa Group SA (E); Danmarks Tekniske Universitet (DK); Universiteit Leiden (NL); Universitaet Stuttgart (D); École Polytechnique Fédérale de Lausanne (CH)

ICAROS NET

Aim:

The objective of ICAROS NET is the development and implementation of a networked interactive computational environment that allows the minimisation of uncertainty in decision-making regarding operational air pollution control and abatement in the urban environment and enhances the coherence in transboundary environmental monitoring.

Partners:

- University of the Aegean (GR); Fraunhofer Gesellschaft Zur Foerderung der Angewandten Forschung E.V., Mcmaster University (CAN); National Observatory of Athens (GR); National and Kapodistrian University of Athens (GR); Space Imaging Europe SA (SIE) (GR); KFKI Research Institute for Particle and Nuclear Physics, Computer Network Centre, Laboratory of Speech Technology for Rehabilitation (KFKL) (HU); Konkoly Thege M UT 29-33 (HU); National Centre of Public Health (HU); Telespazio S.P.A. (TPZ) (I).

* **Shared-cost actions:** participation in shared-cost activities with other successful consortia.

PCE

WINE DB

Aim:

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

Partners:

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

COFAWS

Aim:

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

Partners:

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

CHEM-TEST

Aim:

To develop, in addition to EIS-CHEMRISKS, a tool that supports the General Product Safety Directive and the relevant parts of REACH, by developing missing exposure data and chemical methods from products and articles.

EIS-CHEMRISKS

Aim:

The key objective of this project is to develop EIS-CHEMRISKS as a European-wide expert network animated and operated by the JRC to systematically exchange and assess information on emerging issues related to "Risks from chemicals released from customer products / articles".

HARMONOISE

Aim:

To develop methods by which the sound power output and the directivity of sources of road and rail traffic can be described and assessed as an accurate physical quantity which is independent of short distance sound propagation, including establishment of a correlation with future legislation on limiting the noise generation, set up of data base.

Partners:

- AEA Technology Rail BV (SP); Swedish National Testing and Research Institute; Transport Research Laboratory (UK); VTI, Swedish Road and Transport Research Institute; Technical University of Gdansk, Autostrade (I); TNO Institute of Applied Physics (NL) (non-exhaustive list)

MEDEO

Aim:

To develop methods based on NMR and isotopic techniques and tested for detection of adulteration of olive oil.

Partners:

- Instituto de la Grasa (CSIC) - Sevilla (E); Eurofins Analytics - Nantes (F); Central Science Laboratory- York (UK); CNR - Roma (I); Istituto Elaiotecnica Pescara (I); Stazione Sperimentale degli Oli e Grassi (SSOG)- Milano (I); National Hellenic Research - Athens (GR)

FOODMIGROSURE

Aim:

To develop physico-chemical migration models of migration processes from plastics to real foodstuffs as a tool for estimation of consumer exposure from food contact materials.

Partners:

- Fraunhofer Institute of Process Engineering and Packaging, Freising (D); Central Science Laboratory, Dep. Food Environment & Rural Affairs, York (UK); FABES Forschungs GmbH für Analytik und Bewertung von Stoffübergängen (D); Pira International, Leatherhead (UK); University Santiago de Compostela, Dpto. Química Analítica, Nutrición y Bromatología of the Facultad de Farmacia (ES); Vienna University of Technology, Inst. Food Chemistry and Food Technology (A); Nestlé Research Center, Lausanne (CH); European Chemical Council; Bureaux International aux Techniques (BE)

PICADA

Aim:

To test the photo-catalytic activity of TiO_2, added to different building materials (concrete etc.) for its ability to induce degradation of inorganic (NO, NO_2, O_3) and organic compounds (VOCs).

Partners:

- Italcementi Group - Bergamo (I); University of Thessaloniki (GR)

SPREADS

Aim:

To study NMR measurements for detection of adulteration of spreadable fats.

Partners:

- Universität für Bodenkultur (A); Bundesanstalt für Milchforschung (D); Unilever Nederland BV (NL); Mylnefield Research Services LTD (UK)

EIS-EMF

Aim:

To set up a European Information System on public health protection issues related to Electromagnetic fields (EIS-EMF) as a common basis for decision makers to increase the coherence of the approaches taken in the various Member States and help restore public confidence.

Partner:

- Research Centre Seibersdorf (A)

GC-IRMS

Aim:

Feasibility study for establishment of reference materials for the gas chromatography isotopic ratio mass spectrometry.

Partners:

- Eurofins Analytics - Nantes (F); Central Science Laboratory - York (UK); INETI - Lisboa (P)

INDEX

Aim:

To create a network of European scientists in the area of indoor air pollution and the herewith-associated health impacts.

Partners:

- Federal Environmental Agency Germany (UBA); National Institute for Health (KTL Kuopio, FIN); University of Aarhus (DK); Ospedale Luigi Sacco (I); Department of Psychology Stockholm University (S); Sustainable Development Department, Health and Building Division (F); University of Athens Energy Physics Department (Gr); University College Dublin (IRL)

QASUME

Aim:

The development of a new approach for facilitating Quality Assurance of solar ultraviolet spectral irradiance measurements presently carried out in Europe. In this frame a transportable Unit, developed and hosted at the PCE Unit, which, after thorough testing and validation, will be visiting European UV stations to acquire spectral measurements of global solar irradiance that will be compared with those of the local spectroradiometers.

Partners:

- Laboratory of Atmospheric Physics, Aristotle University of Thessaloniki (GR); University of Innsbruck (A); University of Manchester, Institute of Science & Technology (UK); Institute for Meteorology and Climatology, University of Hannover (D); National Institute for Public Health and the Environment (RIVM) (NL); Finnish Meteorological Institute (FIN).

EDUCE

Aim:

To investigate the ultraviolet (UV) radiation climate in Europe.

Partners:

- Institute for Meteorology and Climatology, University of Hannover (D); Norwegian University of Science and Technology; Institute for Geophysics, Astrophysics and Meteorology, University of Graz (A); Finnish Meteorological Institute; British Antarctic Survey; Laboratory of Atmospheric Physics, Aristotle University of Thessaloniki (GR); National Institute of Public Health and the Environment (NL); University of Manchester Institute of Science & Technology (UK); University of Innsbruck (A); Solar and Ozone Observatory - Czech Hydrometeorological Institute (CZ); Institute of Geophysics - Polish Academy of Sciences (PL); Tartu Observatory (Estonia) (non-exhaustive list)

BMS

EVIGeM (virtual Institute)

Aim:

The European Virtual Institute of Geometry Measurement (EVIGeM) consists of a linked group of European partners, committed to assist and help members and any external customer on all kind of problems concerning geometry measurements.

Partners:

- BIBA (D); Knapp (CH); Mahr (D); Unimetrik (E)

BIOGRAD

Aim:

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

Partners:

- Lima Lto (I); Ceramtec (D); HIP Bodycote (UK); University of Leuven (B); Helsinki University of Technology (FIN); LEMI (F); Josef Stefan Institute (SLO); Nuclear Physics Institute (CZ)

PLASMATECH

Aim:

The PLASMATECH network intends to co-ordinate European activities in the field of Plasma Technologies in order to develop and apply them to the domains of Textile, Health, Food and Environment. In particular, its main objectives are to concentrate all the RTD activities on plasma technologies scattered in EU zone and at a development stage, to promote knowledge transfers, discussion and exchange of information in the consortium, to monitor the production of scientific advice world-wide, to conceive and evaluate potential new niche applications with added value, to generate new developments through projects contracted between partners, and to share knowledge leading to best practice and new standards. The Plasmatech network contains 47 partners from 12 different countries distributed equally in the four fields of interest.

Partners:

- Institut Français du Textile et de l'Habillement (IFTH) (F); Nodal Consultants (F); Dow Corning Plasma Solutions (IRL); Fraunhofer Institute for Manufacturing and Advanced Materials (IFAM) (D); IFP Research AB (S); University of Durham (UK); Eltro GmbH (D); Europlasma N.V. (B); Axcys Technologies (F); Industrias Texteis Somelos SA (P); Chargeurs Group CREAT (F); Saati Print (I); Biomatech SA (F); Università di Bari - Dipartimento di Chimica (I); University of Jena - Institute of Material Science (D); Università di Catania - Dipartimento di Scienze Chimiche (I); CSM Instruments (CH); LCC Engineering & Trading GmbH (CH); Arjo Wiggins (F); Metec Tecnologie Snc (I); CSMA Limited (UK); Absys (F); Robert Bosch GmbH (D); Université Pierre et Marie Curie - École Nationale Supèrieure de Chimie de Paris (ENSCP) (F); University of Bochum (D); University of Stuttgart - Institut für Plasmaforschung (D); Consejo Superior de Investigaciones Científicas (CSIC) - Instituto de Ciencia de Materiales de Sevilla (E); Biophy Research (F); MAT PlasMATec GmbH (D); Sidel (F); Tetrapak (CH); Environment Park (I); Institut für Niedertemperatur – Plasmaphysik (INP) (D); Centro Ricerche Fiat (I); Advanced Energy Industries GmbH (D); Charles University (CZ); University of Patras (GR); Aixtron AG (D); Air Liquide (F); Renault (F); Plasma Air AG (D); Laboratoire de Physique des Gaz et des Plasmas LPGP – CNRS (F); EDF (F); Muegge Electronic GmbH (D); Plasso Technology (UK); University of Milan Bicocca (I).

STERIPLAS

Aim:

Study and validation of an advanced plasma sterilisation process.

Partners:

- Arjo Wiggins (F); R. Bosch GmbH (D); Metal Process (F); Biomatech S.A. (F); C.I.R.M. (I)

IFCA

Aim:

Immunoprobes for Food Contamination Analysis (IFCA).

Partners:

- École Nationale Supérieure de Chimie de Paris (F); Universidad de Vigo (E); Innosense SpA (I); LCC (CH); Abkem (ES); CSMA (UK)

MEDPHOT

Aim:

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

Partners:

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

LAPLADIS

Aim:

Large Area Plasma Etching Process for Display Applications.

Partners:

- FIAT (I); THOMSOM (F); FHR (D); EUROINKS (I)

SPOTS

Aim:

Standardisation Project for Optical Techniques of Strain Measurement.

Partners:

- University of Sheffield (UK); Optical Metrology Innovations (IRL); Ettemeyer AG (D); NPL Management Ltd (UK); SNECMA Moteurs (F); Honlet Optical Systems GMBH (D); Politechnika Warszawska (PL); CRF Società Consortile per Azioni (I); Eidgenössische Materialprüfungs- und Forschungsanstalt (CH)

Structural Monitoring of the Duomo of Como using Optical Fibre Bragg Grating Sensors

Aim:

To install a remote automated monitoring system and a network of sensors (~1000m of optical cable) based on optical fibre Bragg gratings for continuous measurement of temperature and relative displacement. A data report file is sent by email every day. The raw data are entered in a database, transformed into tables and diagrams in order to display the structural status of the cathedral, and made accessible on internet to authorised persons to be exploited by engineers and decision makers.

Partners:

- Comitato per la Salvaguardia del Duomo di Como, Amministrazione Provinciale di Como (I); Politecnico di Milano (I).