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Mission

The mission of the IHCP is to support EU policies for health and consumer protection. The Institute carries out research to improve the understanding of the hazards, exposure and risks posed by food contaminants, drugs, chemicals, products, services and systems and to develop, validate and apply advanced methods and strategies of high scientific quality.
The first year of operation of the Institute for Health and Consumer Protection, the newest Institute of the JRC has just ended. The Institute aims to play a leading role in support of EU policies in emerging areas of health and consumer protection in order to offer the citizens an improved, predictable and efficient regulatory environment based on solid scientific foundations. It was formed at the end of 1998 by clustering and re-organising expertise and structures spread through various JRC Institutes, in order to provide a common umbrella for the more effective use of the JRC scientific and technological competencies in the areas.

During 1999, it has gone through a phase of natural evolution, on both scientific and organisational aspects. In the start up phase, great efforts have been spent for establishing the basis for the future Institute development by setting up strategic orientations and establishing objectives, rationalising the staff table and providing the needed infrastructure. Nevertheless, the year 1999 has already been a very fruitful one in terms of the scientific results produced, as it will be apparent from the range and scope of projects you will find described in this report.

In short, the IHCP aims at establishing itself as a reference point in the European Union for the development and validation of methods to guarantee the safety and quality of commercial goods such as food products, animal feed, medicines, chemicals as well as services and systems, which are parts of our living environment.
JRC and the IHCP

The JRC is a Directorate-General of the European Commission. It has its headquarters in Brussels and eight Institutes located on five separate sites in Belgium, Germany, the Netherlands, Spain and Italy.

The Institutes are:

- The Institute for Reference Materials and Measurements (IRMM), Geel, Belgium
- The Institute for Transuranium Elements (ITU), Karlsruhe, Germany
- The Institute for Advanced Materials (IAM), Petten, the Netherlands
- The Institute for Prospective Technological Studies (IPTS), Seville, Spain.

The largest site is located in Ispra, Italy, hosting four Institutes:

- The Institute for Health and Consumer Protection (IHCP)
- The Institute for Systems, Informatics and Safety (ISIS)
- The Environment Institute (EI)
- The Space Applications Institute (SAI).

The IHCP was created in 1998 to provide a single body to assist EU policy makers in the various fields of health and consumer protection—such as food, chemical and pharmaceutical safety, reliability of medical implants and advanced diagnosis techniques (including imaging) and electronic commerce, particularly with particular reference to health matters.

The IHCP serves the citizen by establishing clear standards and developing methods to guarantee the safety and quality of food, chemicals and pharmaceuticals, and to assess the reliability of biomedical devices and diagnosis techniques. Its activities include the assessment and management of risks and the provision of reference information services in support of the EU policies. The IHCP contribution to an improved regulatory environment is in addition relevant to industrial competitiveness.

The IHCP is particularly active in:
1. Analytical methods for food safety and quality.
2. Alternative test methods for regulatory toxicology testing – it is an international reference centre for validation of advanced methods (e.g. in vitro) of relevance in the various fields of biosciences.
3. Chemical information and risk management
4. Research on biomaterials and the reliability of biomedical devices, as well as use of advanced diagnostic methods in health applications
5. Information and communication systems for pharmaceutical regulation.
Units statements
Management Support
HEAD OF UNIT: GIAMPIERO TARTAGLIA

The MS Unit guarantees the optimum use of human and financial resources within the Institute, for the achievement of its scientific aims, through co-ordination of the IHCP horizontal tasks in the areas of Management, Information/Communication, Marketing, Information Technology services and Safety and by provision of the necessary administrative and infrastructure support. The Unit acts as interlocutor with the horizontal JRC Directorates (Directorate General, Programmes, Administration) and provides the guidelines for the internal and external flow of information and for the general organizational questions.

Food Products & Consumer Goods
HEAD OF UNIT: ELIKE ANKLAM

The role of the FR&CG Unit is to develop, harmonize and validate analytical methods in the areas of food safety, food quality and required to assure the European citizen safety of consumer products. In these areas the Unit carries out research, furnishes specialized information services, acts as a scientific interlocutor and advisor for emerging issues, and implements and supplies scientific services for monitoring chemical, physical and biological data. This work is carried out in support of European policies to ensure protection of the consumers in the food area, to prevent and monitor fraud and to establish labelling compliance for novel food items or high-quality products.

Toxicology and Chemical Substances/European Chemicals Bureau
HEAD OF UNIT: GERALD VOLLMER

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

Validation of Biomedical Testing Methods/European Centre for the Validation of Alternative methods.
HEAD OF UNIT: MICHAEL BALLS

The European Centre for the Validation of Alternative Methods (ECVAM) seeks to promote the scientific and regulatory acceptance of alternative methods in toxicology studies and, in general, in the several fields of biosciences through research, development of new tests and their validation, and the provision of specialized information services, with the aim of contributing to the refinement, reduction and/or replacement of laboratory animal procedures. ECVAM co-ordinates the independent evaluation of the relevance and reliability of tests (e.g. in vitro tests) for specific purposes, and in particular through prevalidation and validation studies so that chemicals and products of various kinds, including medicines, vaccines, other biologicals, medical devices, cosmetics, household and agricultural products, can be manufactured, transported and used more safely, while the current reliance on animal test procedures is progressively reduced.

Biomedical Materials and Systems
HEAD OF UNIT: HERMANN STAMM since May 2000

The BMS unit conducts thematic research on the development, validation and use of advanced processing techniques and test methodologies for bio-compatible materials, bio-medical devices and related to the use of radio-tracers in Nuclear Medicine and for release studies related to consumer goods. The monitoring role of the BMS Unit, undertaken in collaboration with regulatory bodies, health care organizations and industrial partners, will be used to supply EU policy makers and other interested parties with reliable and critically assessed processes, methods and information on emerging fields in medicine and other consumer related issues.

Support to Pharmaceutical Regulation
HEAD OF UNIT: FLAVIO ARGENTESI

The SPR Unit provides an important contribution for improvement of the organization, management and dissemination of sensitive information in the pharmaceutical field and in other consumer protection areas. Its work is focused on the research, development and harmonization of Communication Systems for regulatory tasks in the areas of pharmaceuticals for human and veterinary use.
Scientific Highlights

- Co-ordination of validation studies, at European Level, for the detection of Genetically Modified Organisms (GMO) in food stuffs (soybean, maize), including, in collaboration with the Institute for Reference Materials and Measurements (IRMM) of the JRC, the preparation and evaluation of reference materials.

- Simplified methods for the determination of polychlorinated biphenyls (PCBs), the source of the recent contamination of Belgian food and feeds with dioxin, have been set-up as a support to the Belgian laboratories.

- Participation in a validation study to evaluate the migration of phthalates from toys, which may be chewed and gnawed by small children. In addition, a prototype mechanical facility has been developed to provide a more representative simulation of the migration of phthalates into the mouths of children.

- In 1999, the International Uniform Chemical Information Database (IUCLID), which is developed and maintained by ECB was adopted by the International Council of Chemical Associations (ICCA). This is a major step forward in standardisation as the World Chemical Industry will now use the IUCLID database to collect and distribute data on chemical substances and to increase the accessibility of information on chemicals.

- An innovative model based on genetically-engineered neuronal cell lines for pharmacotoxicological testing has been patented and will allow elucidation of mechanisms of neurological disorders or neuromuscular diseases.

- A pilot version on-line quality procedure system (OLIVE® JRC) for in vitro toxicological work was successfully developed, which will facilitate the implementation of the OECD Good Laboratory Practice (GLP) principles in in vitro toxicological studies. OLIVE® JRC is copyright protected and a trademark has been applied for.

GLP On-Line in vitro Toxicology
ECVAM organised the 3rd World Congress on Alternatives and Animal Use in the Life Sciences, held in Bologna, Italy, from 29 August to 2 September 1999. This was a major international event, which attracted about 800 scientists, including 30 from the JRC, and will reinforce the reputation of ECVAM, the IHCP and the JRC in the biosciences field.

An apparatus enabling plasma treatments of the inner parts of flat hollow substrates and of small diameter tubes in a uniform way has been developed at the IHCP. A patent application has been submitted. This treatment can be used for various medical applications – catheters, endoscopes for medical materials - and also in food or pharmaceutical packages.

An original inductive plasma source has been developed, allowing homogeneous heat treatment of flat surfaces of large dimensions. The availability of this technology is thought to find promising outcomes in the field of Flat Panel Displays (FPD), an activity that is to be conducted in collaboration with the major European manufacturers in this field.

Prototypes of the Unified Tracking System (UTS) and of the Medicine Analysis Network for Europe database service (MINE 1) were developed in 1999 at the IHCP.

- The UTS system aims to track the process of evaluation and marketing authorisation of medicinal products in Europe, and was developed as support to the European Agency for the Evaluation of Medicinal Products (EMEA), the Enterprise DG and Member State authorities concerned with the marketing of medicines.
- The MINE 1 databases gather all associated information on scientific efficacy and safety of medicinal products marketed in Europe.
Scientific Co-operation

The IHCP develops and exploits networks of partners and collaborators. These partnerships extend the IHCP reference function in the areas of safety and quality of food, chemicals and pharmaceuticals, and reliability of biomedical devices and diagnosis. This is achieved through the pooling of scientific competencies, facilities as well as knowledge resources with those of its partners and by tapping the resulting expertise, in order to contribute to the implementation of EU policies in these areas.

In the areas of food safety and quality, GMOs, chemical risk assessment and marketing authorisation for pharmaceuticals the IHCP has well-established links and collaborations with EU governmental bodies, Non-governmental Organisations, Member States enforcement laboratories and academia in the member States as well as with relevant industries and industrial associations. Furthermore, it maintains strong contacts and relationships with academies and R&D laboratories, both public and private, on research, development and validation of advanced techniques in the areas of in vitro tests, biomaterials and biomedical implants and information technology tools developed to support information dissemination. International interlocutors of the IHCP include the bodies of the OECD, EFTA countries (Norway, Switzerland, Iceland), eastern European countries and in the USA, Canada, Japan or Australia.

- EU Union
  Commission Directorates General
  Governmental Bodies
  Member State Laboratories
  Universities and Research Institutions
  Industry and Industrial Associations

- EFTA Partners
  Norway
  Switzerland
  Iceland

- Eastern European Countries
  Czech Republic
  Estonia
  Hungary
  Poland
  Slovakia
  Slovenia

- Outside Europe
  USA
  Canada
  Australia

Organisation for the Economical Co-operation and Development (OECD).
Industries – Chemicals, Pharmaceuticals, Biotechnology, Agricol
The IHCPin figures 1999

Work programme

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Competitive Actions

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<tr>
<td>Total</td>
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Managerial Highlights

Administrative

The IHCP is deeply involved in competitive actions through its participation in research and pre-competitive scientific activities (e.g. Shared Cost Actions) within the EC Fifth Framework Programme and through provision of research and scientific services to third parties.

IHCP Institutional Budget in 1999 – breakdown per project (Missing)
- Staff details, (charts in annex)
- Reference to Competitive Actions,

List those gained during the 5th Framework Programme.

The implementation of Total Quality Management (TQM) tools in the IHCP was a major managerial commitment during 1999. Several initiatives were undertaken in this period, including the release of the IHCP Project Management Manual, Strategy document and Business Plan and the launch of the self-assessment exercise within the IHCP, using an approach based on the general model of the European Foundation for Quality Management (EFQM). As a follow-up, self-assessment teams were formed on... with tasks to be carried out in the first half of 2000.

Communication was an area where the IHCP was intensively involved at a JRC level. These included the participation of IHCP staff in the launch of the 5th Framework Programme of the European Commission held in Essen (Germany) in February 1999 and in the Launch Event of the specific JRC Activities connected with the 5th Framework Programme, held in Ispra in March 1999.

A considerable effort was made by the Institute in the preparation of a contribution for the JRC@EP event, organised by the JRC Information & Public Relations Unit, to be held in early 2000 at the European Parliament in Brussels.
In 1999, an IHCP brochure was issued, in which the Institute organisation and activities are presented. A series of leaflets describing individual projects of the IHCP was also produced, in collaboration with the JRC Information & Public Relations Unit.

The scientific units of the Institute received wide press and media coverage – seven press releases were produced with JRC Brussels on Genetically Modified Organisms (GM0s), Food Safety, Chemicals Databases, and validation of alternative methods. Wide coverage has been given, at an International level, to IHCP activities on food safety, GM0s, biomedical materials and devices, releases from food packaging or consumer products and the Third World Congress on Alternatives and Animal Use in Life Sciences, held in Bologna in September 1999, organised and hosted by the ECVAM Unit of the IHCP, in collaboration with the JRC Information & Public Relations Unit. In particular, international broadcasting companies such as BBC, RAI and Euronews, and representatives of the press such as Science and Corriere della Sera have visited the institute and reported its activities.

An IHCP website (http://ihcp.jrc.it) is available on the Internet. It provides, in the present version, a general description of the institute in the sections Overview (Mission and Objectives; How to Arrive and General Contacts), Organisation (description of the IHCP Organisational Units) and Activities (IHCP Institutional Projects). Significant results and other up-to-date information on the Institute are given on the News section and a access to information services available at the IHCP is provided in the Services section.

Training actions in which IHCP staff participated, were mainly on scientific and technical topics (20 courses out of a total of 23), in particular, related to the use of information technology tools in scientific and technical work. Additional Scientific and Technical courses covered subjects related to IHCP activities – Toxicology, cell cultures, update on theoretical aspects relevant to biomaterials or food studies or addressing new activities such as biomedical devices and packaging, and contamination control in clean rooms, used for the production of radio-tracers and activities on radio-pharmaceuticals.
Collective actions undertaken at the IHCP focussed on scientific and technical subjects relevant to identified service needs, including laboratory methods: with courses on Oil Hydraulics, organized by the Biomedical Materials and Systems (BMS) Unit – Mr. R. Stroosnijder, and on Good Laboratory Practices for in vitro toxicology, organized by the European Centre for the Validation of Alternative Methods – ECVAM Unit, co-ordinated by Mrs. S. Coecke. A series of eight seminars on Positron Emission Tomography (PET) technology was also organised. The topics covered by these training activities included all themes of Nuclear Medicine - Production of radio-tracers and radio-pharmaceuticals; PET image modelling; pre-clinical studies and topical clinical applications.

The IHCP Safety, Prevention and Protection Service set-up a Training Plan on Safety for the Institute. This plan was subsequently revised and expanded by the JRC "Safety Group", which includes representatives of all JRC Institutes and Units (Scientific and Technical services reporting to the JRC Director General) at the Ispra Site. The final training plan of the JRC "Safety Group" was submitted to the JRC Training Office, which is in charge of the co-ordination of the listed actions. The plan consists of a total of thirteen courses, to be held at Ispra during 1999-2000, with three additional courses under preparation. In accordance with this plan, three courses were held in 1999, at Ispra, with participation by about 55 IHCP staff members.

The activities undertaken, in 1999, by the Safety, Prevention and Protection Service were designed to monitor and implement JRC safety recommendations in the IHCP laboratories and buildings. A first set of actions was defined at the beginning of 1999, including the designation of IHCP officers, at Unit level, in charge of safety and accident prevention.

Periodical checks of compliance with the JRC recommendations were carried out, including specific inspections following a hazard-check-list set out in the methodological approach for the whole JRC. Actions to be taken for each laboratory were identified and disposal of unwanted laboratory chemicals was carried out. An IHCP safety manual was issued, which functions as a reference for implementation of the safety procedures required by law, for laboratory work. This manual helps IHCP scientific and technical staff to anticipate potential risks and prevent hazards arising in chemical and other laboratories as well as to establish safe practices in the workplace.

A library of basic safety documentation has been established, covering procedures for handling and storage of dangerous chemicals, pressure vessels (including related hoisting equipment) and lifting devices. Emergency/exit plans for buildings and a selection of EU and Italian legal documents concerned with safety aspects have been provided. Work on safety, prevention and protection is embodied in the "Safety project 2000" plan, aimed at assessing and implementing the necessary actions to ensure that the safety procedures at the IHCP are in conformity with Italian law 626. The implementation of this plan was initiated in 1999 and it is expected that by the end of 2000 an acceptable compliance will be attained.

Changes in the infrastructure of the IHCP carried out during 1999 included the preparatory work, logistical support and the relocation of two Units (around 60 persons) to a new building, which will host the European Chemicals Bureau and Support to Pharmaceutical Regulation Unit. The relocation of these two Units will be concluded in early 2000. This was the major relocation of IHCP staff members dispersed at different locations in the Ispra site. Infrastructure and logistical support was also provided for the planned upgrade of the Microbiology laboratory. Preparatory work for the decommissioning of a number of old IHCP buildings and offices was also carried out. Recurrent services included the support of management and maintenance of IHCP buildings and laboratories, including construction work and logistics.
IHCP Activities

Safety and Quality of Food Products
Releases in Consumer Products and Biomedical Devices
Genetically Modified Organisms.
Validation of Alternative Methods
Medical Imaging Using Radiotracers
Biomedical Devices and Functional Systems for medical applications.
Telematic Systems for the EU Pharmaceutical Regulatory Activity
Consumer Protection on Electronic Commerce
Chemical Substances: Risk Assessment
Safety and Quality of Food Products

Technology permeates today practically every stage of the food chain including crop growth, animal production, food processing and storage. An important trade commodity in the global market, food products and raw foodstuffs risk exposure to contamination, spoilage and adulteration. Not only man-made chemicals or other risks (e.g. frauds) play a role here, also nature itself (e.g. microbiological contamination and natural toxins) can be responsible for contamination during harvesting, transport or storage.

Consumers expect that food is safe, that the food supply is sound and wholesome and that food products are correctly labelled. For regulatory authorities and laboratories with responsibility for monitoring tasks, the challenge is to assess adequately the safety and quality of food products. This requires the availability of reliable tests and methodologies to anticipate and manage risks and to enforce regulatory controls. Moreover, food producers seek clear rules to test the compliance of their procedures and to trade in the single market with the certainty that criteria of a given EU country will be recognised in other Member States.

These issues shape the HCP activities on safety and quality control of food products. The various tasks on this area — studies on natural toxins in different food matrices or foodstuffs, chocolate and wine composition, to name only a few— are carried out in close collaboration with the relevant Commission General Directorates (e.g. Health and Consumer Protection, Environment, Agriculture, Enterprise) and with a wide network of analytical laboratories within the EU. The aim is to suggest harmonised methods and, if required, to improve existing ones and/or to develop tests that can be used for control purposes in the Member States and support regulatory measures at a European level. Moreover, contingency procedures are set at the HCP to handle unforeseen issues requiring swift response in terms of provision of screening methods and analytical services. In 1999, these were deployed in support of the Commission and Belgian laboratories to deal with contamination of food of animal origin with dioxins and their precursors. The commitment to a common scientific framework is reinforced through the provision of screening methods, co-ordination and/or participation in validation trials and monitoring of substances when quality and safety inspection for marketed products is critical.
Natural Toxicants in Food and Feeding Stuff

Mycotoxins are toxic metabolites, produced in nature by fungi that develop in plant materials, and can enter the food chain. They may occur be present in various cereals, nuts, dried fruit and coffee but also in processed food items such as wine and fruit juice. As mycotoxins are found in raw agricultural products, animals are also exposed to contamination and, consequently, safety risks arise for animal derived products (e.g. milk, liver paste). The presence of a particular mycotoxin depends on the food item: Fumonisins are found in maize; aflatoxins may be present in peanuts, figs or milk; ochratoxin A can result in coffee and meat products while patulin can occur in fruit juices. Different types of mycotoxins may be found in a single food item, with health hazards resulting even for very low concentrations. In particular, there is evidence that these compounds can be nephrotoxic (i.e harmful to the kidneys), immune suppressant, teratogenic (i.e causing malformations) and carcinogenic.

Very low limits restricting mycotoxin intake are established by the existing regulations at a European level, with particular attention being paid to baby food. The monitoring of these low concentrations requires the availability of reliable analytical methods. The work at IHCP has included the evaluation of analytical methods for the determination of various mycotoxins – e.g. aflatoxins, ochratoxin A, fumonisins – in several food items as well as development and/or optimisation of tests and subsequent validation.

Particular emphasis has been put on the contamination of corn, fig paste, peanut butter, pistachios and paprika powder with aflatoxins. Effective and accurate quantification strongly depends on the extraction techniques used to discriminate aflatoxins in a given food item. Today, analytical techniques such as high performance liquid chromatography (HPLC) are used after sample clean up using immuno-affinity columns. The latter allow binding of the aflatoxins to specific antibodies present in the clean up column. In this way efficient separation and purification of the aflatoxins in the food sample under analysis is obtained. An approach employing the combined use of immuno-affinity columns and HPLC has been successfully developed and validated by the IHCP for various food products, especially baby food (infant formula) and feed stuff. They are present in the process of becoming official methods at an international level for bodies such as CEN (European Committee for Standardisation) and AOAC (Association of the Official Analytical Chemists) International.

Compliance with European legislation must also be observed for food produced outside the European Union. As mycotoxins can occur in imported goods (food, feed stuff) from developing countries, there is a need to make available swift and reliable methods in these countries. The use of HPLC in these cases has some shortcomings, such as high cost and specialised maintenance. To overcome these difficulties, the IHCP has developed a method for the determination of aflatoxins based on thin-layer chromatography (TLC) after clean up with immuno-affinity columns. This method will be validated through the course of 2000 in collaboration with other international organisations and this will involve laboratories and authorities in developing countries. In addition, the IHCP has developed two prototypes of simplified and cost-effective scanner systems for the quantification of aflatoxins after their separation by TLC and is also investigating alternative systems for the detection of these compounds. After their separation by HPLC, UV irradiation is applied to enhance the fluorescence emission used to quantify the concentration of mycotoxins.
The monitoring work of IHCP is presently focused on ochratoxin A and aflatoxins in European wine samples of different types and in chocolate products.

The thorn apple (Datura sp.) plant is widely diffused, and produces toxic seeds, containing as Datura alkaloids, which can contaminate crop cultures. These alkaloids can impair animal health, when arising in soya beans and flax seeds used for feed stuff production. However, there is also a risk of contamination of the food chain especially in biologically grown crops, as less pesticides are used in this types of agriculture. Official methods to detect the contamination with Datura are based on separation of the thorn apple seeds in the food item under analysis and evaluation of their weight. However, this approach is not accurate, as the amount of alkaloid in the Datura seeds can vary significantly, thus requiring direct assessment of the concentration of toxic alkaloids. This can be very difficult due to the presence of other compounds in the food item under analysis. These foreign compounds are not completely removed during the initial extraction step, making the discrimination of the main alkaloids by HPLC relatively complicated. The IHCP has evaluated in detail those factors critical for efficient separation of alkaloids, in order to identify appropriate sample preparation methods for the HPLC analytical procedure. The establishment of a simplified methodological approach for separation and quantification is currently in development.

### Contaminants in Food and Feeding Stuff

The IHCP has contributed to addressing the concern on contamination by dioxins in food of animal origin, which arose in mid-1999 in Belgium. Test protocols based on two simplified methods for the determination of polychlorinated biphenyls (PCBs) were swiftly established and supplied to Services of the European Commission. PCBs had been identified as the source of that particular contamination of meat.

Alternative screening methods (e.g., using time-resolved fluoroimmuno assay), which have the advantage to increase the throughput of food samples’ analysis, are under development and validation at the IHCP. In addition, during 1999, the IHCP analysed about 500 samples of animal derived food products (e.g., meat and milk powder) to determine the concentration of PCRs. This was done to check if the food items were compliant with the maximum limits (200 ng/g fat) established by the European Commission in 1999. This work was carried out for the European Union within the framework of humanitarian help Programmes.

A monitoring programme has been developed to assess the capability of different European laboratories to carry out analysis of foods and feed stuffs with respect to the content of compounds such as PCBs or dioxins. The IHCP is participating in these activities, aimed to setting up of proficiency tests in the various laboratories through the provision of the necessary test protocols, sampling plans and support for statistical data evaluation. This work is carried out in close collaboration with the IRMM (JRC-Geel), which provides the necessary reference materials to be used within this programme. The presence of unsafe meat and bone meals in feed stuff is suspected to be the possible cause of bovine spongiforme encephalopathy (BSE) in farm animals. In some feedstuffs, used for poultry and pigs, it is believed that the biological agents triggering these unwanted effects are destroyed through appropriate heat treatment of animal meal. The activities of the IHCP in the area of feed stuff are directed towards the provision of reliable methods to confirm that suitable treatments have been carried out and enable, at the same time, the measurement of harmful components in animal meals.

A test based on enzyme linked immunosorbent assay (ELISA) has been assessed to monitor that appropriate heat treatment and sterilisation has been carried out for animal ingredient constituents of feedstuffs. The Food Products and Consumer Goods Unit already coordinated in 1998 a validation of this method in collaboration with 21 laboratories from 12 European Countries. This study has evidenced that the method is sufficiently accurate to confirm that heat treatments (temperatures > 1330 C) for animal meals have been properly carried out, before their use for the production of feedstuffs. Measurements in a commercial rendering plant (where ingredients of animal origin are processed before being used for feedstuff production) and in-house investigations at IHCP have confirmed the conclusions of the ELISA test evaluation.

Additional work on development and validation of methods are under way to detect and quantify animal components in feedstuffs. The aim is again, to confirm that the animal meals were correctly treated and steri-
ised, but the focus is now shifted to the final product. The development of sample collection schemes for these analyses will also be pursued, to ensure correct assessment of large production quantities and different production series of feedstuffs.

**Pesticides in Food**

A monitoring programme, co-ordinated at a European level, aims to estimate the concentration of certain pesticides in food, in particular, with respect to the maximum residue levels (MRLs). It considers the analysis of specific food items collected in all Member States on a random basis. These studies are strongly dependent on the reliability of the selected analytical methods and of the sampling methods used in the Member States. The IHCP is contributing to this programme through assessment of the sampling methods used in the different Member States, by providing support for the establishment of thorough competences in the laboratories involved and by carrying out the statistical evaluation of the data derived from the monitoring programme.

The IHCP has set up a laboratory for the analysis of pesticides in food in order to strengthen scientific and technical support to the EU pesticides monitoring programme.

**BEVABS - European Office for Wine, Alcohol and Spirit Drinks.**

The work undertaken at the European Office for Wine, Alcohol and Spirit Drinks (BEVABS) ensures effective control of major fraud (e.g. sugaring and watering) in the wine sector, including false declarations of geographical origin, at a European level. Created in 1993, BEVABS manages an EU wine database on authentic wines. The database stores and manages data on the ratios of stable isotopes present in the alcohol (ethanol), measured after wine distillation, information on the geographical origin, year of production, type of grape, wine making process, chemical analytical data, soil composition and weather conditions. At present, it stores information on more than 15,000 wines, with quality control of the data supplied by the member states also carried out at the IHCP. In 1999, the data on the 1998 vintages was included in the BEVABS database, and work on the 1999 vintage was initiated. In addition, BEVABS performs complementary analytic tasks for four Member States, in which technical capabilities are not available. BEVABS has analysed wines and other alcoholic beverages collected in the European Market at the request of the Commission's Anti-Fraud Office (OLAF). Improved software installed in 1999 now allows use of new user- graphic interface with improved user features and will include data submission/retrieval of new isotopic parameters likely to be considered for future officially approved methods.

**Chocolate**

Chocolate is composed mainly of cocoa mass (liquor), cocoa butter, sugar and lecithin. In some Member States, the use of some vegetable fats, the so-called cocoa butter equivalents, is accepted in the production of chocolate. Cocoa butter equivalents have similar chemical and physical properties as cocoa butter. The use of these additives has been regulated by the recent EC Directive on Chocolate, where the use of certain specific vegetable fats (Illipe, palm oil, sal, shea, kokum, and mango kernel) in chocolate is allowed. In particular, a maximum concentration of 5% for cocoa butter equivalents is permitted thus creating a need for reliable analytical methods to quantify these compounds (including mixtures) in chocolate.

The IHCP has developed and validated appropriate analytical methods for the determination of such vegetable fats and made a final report supplied to the European Commission in 1999. Ensuing activities on chocolate, undertaken in 1999, addressed the evaluation of meth-
ods to check compliance of products labelled with the statement "Does not contain vegetable fats", effects of milk fats on analytical results and a survey of methods to detect cocoa butter equivalents exhibiting antioxidant properties (e.g., polyphenols).

Dairy Products

Throughout 1999 the IHCP was actively involved in studies aimed at the authentication of butterfat and the determination of the water content in products such as milk powder. No reliable analytical method is available to determine the true water content in food. This is because most of the official methods, presently available, rely on the determination of water and other substances in volatilisation processes, which do not lead to reproducible results when carried out in different laboratories. To promote a wide exchange of views on these problems, the IHCP organised the first international conference on "Water determination in food - a challenge for the analyst" in April 2000. In addition, assistance was provided to the IRMM in a collaborative trial study to qualify four different methods for the determination of water in milk powders produced in different European Member States.

Honey

At a European level, since 1974, Community Directive 74/409 defines the composition and production of honey. More recently, the European Commission has proposed an amendment to this Directive to include information on the botanical and geographical origin. In support of the implementation of this amendment, the IHCP has been involved in the identification and assessment of methods to enable label compliance controls for honey products in the European Market. In 1999, a study of the performance of various analytical techniques to determine the botanical and geographical origin of honey was concluded and the final report of this study forwarded to the pertinent Services of the European Commission. In this study, fifty two types of honey from eight different EU countries and obtained from ten distinct botanical sources were considered. It should be noted that these results were obtained for a relatively limited set of honey samples, and future studies should be extended to a broader series of honey products. A further support for quality control tasks would be the establishment of a databank of honey samples, having well-defined geographical and botanical origins.

As a complement to the above study, a marker compound for strawberry-tree honey has been isolated and identified using Mass Spectrometry and Nuclear Magnetic Resonance. This compound (2,5-dihydroxyphenylacetic acid) was not detected so far in other monofloral honeys and can be used as "fingerprint" for those types of honey derived from this botanical source and can be traced by analytical methods for labeling compliance.

Olive Oil

The higher costs of oils derived from olive fruits and their "brandname" value, generally related to geographical origin, can lead to commercialisation of olive oils containing lower grade and cheaper edible oils and consequently of mislabelled products. Adulteration is very often difficult to detect using conventional analytical methods. The approach developed at the IHCP to address this problem is based on the measurement of the ratios of stable isotopes in combination with chromatographic analysis and nuclear magnetic resonance spectroscopy.

Particular emphasis has been placed on the detection and quantification of added hazelnut oil to olive oils. Various methods for the quantification of foreign oils in olive oil were investigated. Initial work was carried out using isotopic analysis - Nuclear Magnetic Resonance (NMR), continuous flow isotopic ratio mass spectrometry (CF-IRMS) - coupled with high-temperature gas chromatography (HT-GC). These techniques were used to establish the triglyceride profiles for oils of different vegetal origin. Analysis of the data obtained with NMR allowed the detection of olive oils adulterated with hazelnut oil.

Preliminary results of the application of stable isotope ratio analysis to olive oils - measuring the fractions of 13C and 18C from Olea Europea L. fruits, coming from Italy, Greece, Spain and from southern Mediterranean countries (Morocco, Tunisia, Turkey) - allowed a qualitative distinction of the different climatic areas in which the fruits are grown.
Selected Publications


TECHNICAL EUR REPORTS


Web Information resources

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

At the Food Products & Consumer Goods Unit Site:
Food safety: http://food.jrc.it/activities/safety/index.htm
Food quality: http://food.jrc.it/activities/quality/index.htm
European Wine Databases: http://food.jrc.it/activities/bevweb/index.htm
lead to individual pages on each substance. Each page shows the availability of methods and/or spectroscopic information (mass spectra, infra-red spectra and NMR spectra) that can be downloaded as portable document files.

Regulatory documentation and additional information on Food Contact Materials was made available at the URL: http://cpf.jrc.it/webpack/. The contents and overall hyperlink navigation of this website will be reformulated in 2000, in order to include new documents and enhanced information access solutions to an ever increasing number of European regulatory documents and their related information.

Transfer of reference collections of monomers and additives used in food contact material from two Member States’ laboratories (NL, UK) to the Food Products and Consumer Goods Unit was performed as part of the effort aimed to the establishment of a European database and materials bank. The laboratory participated successfully in an international performance testing scheme, which endorsed the accuracy and value of the research performed in the area of food contact materials.

**Migrations from toys and childcare articles**

The migration of potentially harmful substances from toys and childcare products to physiological fluids (e.g. saliva) raises important safety concerns. A primary issue is related to the health consequences of migration of phthalates, used as softener in soft polyvinyl chloride (PVC), which is a common component of articles used by children. One of the main difficulties on the assessment of the hazards associated with phthalate migration is the lack of methods that reproduce, in a realistic manner, the chewing and gnawing processes associated with the use children make of these PVC articles.

At the IHCP, studies of the migration of phthalates from childcare products were carried out using mechanical simulators. Methodologies adopted in Member States laboratories were employed, such as horizontal shaker devices and head-over-heels agitators. In these test systems, test samples are immersed in solutions of simulators of physiological saliva. In addition, an "in-house" concept for a particular mechanical gnawing/chewing solution was designed and a prototype mechanical simulator, based on this concept, was constructed. Studies carried out in 1999 focussed on comparisons between horizontal or head-over-heels shaking approaches with the "in-house" gnawing/chewing simulation methodology. Future activities are aimed at refining the testing procedures in order to determine a set of migration rates and concentrations over time, representative of the physiological processes associated with phthalate intake by children, and to be used in identification of hazards and to for risk assessment.

The Food Products and Consumer Goods Unit participated in a restricted round-robin test on phthalate migration from samples representative of PVC toys, baby bottles and pacifiers. Standard model discs to mimic toy materials as well as samples obtained from commercial toys were considered and six European laboratories participated in this round robin. A comparison of different methods for studying the migration of Bisphenol A in baby bottles was also initiated.
At the IHCP, studies of the migration of phthalates from childcare products were undertaken by employing the use of mechanical simulators. Studies considered methodologies adopted in Member States Laboratories, such as horizontal shaker devices and head-over-heels agitators, where test samples are immersed in solutions of simulators of physiological saliva. Further, an "in-house" concept of a particular mechanical gnawing/chewing solution was designed and the prototype mechanical simulator, based on this concept, was constructed. Studies done in 1999 focussed on comparisons between horizontal or head-over-heels shaking approaches with the "in-house" gnawing/chewing simulation methodology. Future activities are aimed at refining the testing procedures in order to establish a set of migration rates and concentrations over time, representative of the physiological processes associated with phthalate intake by children, likely to be used in identification of hazards and to be used for risk assessment.

The Food Products and Consumer Goods Unit has participated in a restricted ring test on the phthalate migration from samples representative of PVC toys, baby bottles and pacifiers. Standard model disks to mimic toy materials as well as samples obtained from commercial toys were considered and six European laboratories were involved in this assessment. A comparison of different testing methods was made.

High sensitivity studies in food contact materials and biomedical implants.

Hazards resulting from release of materials or chemical substances from products such as medical devices and consumer goods are difficult to establish, when the concentrations of the released substances are quite small but yet critical in view of the long-term use. These concerns include migrations and contamination during use of food or pharmaceutical packaging, jewellery, and child-care products as well as materials or chemicals released from medical implants.

The IHCP carries out a large amount of research on release due to surface degradation of materials and devices under conditions relevant to their utilisation, using a combination of advanced techniques. In particular, highly sensitivity electrochemical and nuclear (i.e. using radio-tracers) analytical methods can be applied to measure the release of compounds during simulation of practical use. These activities are undertaken along four lines of activity: pre-normative research in support to the "nickel directive" 94/27; pre-normative research on chemical release during food processing; development of release methods with high spatial resolution and evaluation of emerging needs (watch-alert task) regarding release evaluations on food packaging.

In 1999, the activity in support to the "nickel directive" 94/27 comprised systematic studies on different products regarding release of nickel as a function of relevant test parameters, including environmental (pH, different chemicals for adjustment of pH, influence of lactic acid and urea), test time and statistical scatter on multiple samples. Various experimental factors showed a significant effect on the release rates, which is an important point in the discussion on the relevance of the draft CEN norms, which will become available in 2000. The need for action on production of reference materials to be used in this study was considered.
An Electrochemical Thin Layer Activation Facility (ETLAF) was used to examine the low level release of metals during food processing. ETLAF combines conventional electrochemical testing with radio-tracer methodologies, available at the IHCP-Cyclotron, for the study of corrosion processes, providing a highly sensitive, real-time, monitoring of metal release into liquid food products. ETLAF was used in the assessment of nickel and chromium release from steels encountered in the large-scale production of glucose syrups. Studies using Thin Layer Activation (TLA), due to its area selectivity, have demonstrated that experimental artefacts might significantly influence measured release rates. Additional activities have considered effects of the mechanical deformation on corrosion behaviour of alloys, which are relevant to a wide range of applications where commonly used metal alloys, in both production plant and in food packaging, are placed in contact with food products. Regarding the nickel content of stainless steels, the potential Ni release during food processing or from consumer goods is critical. Studies were undertaken showing that the deformation of the material during the production of utensils for example might significantly influence the corrosion and thus this factor should be considered for test protocols in this framework. Since the overall release might be dominated by locally occurring processes, development of release detection methods with high spatial resolution is being undertaken. The use of TLA to assess release from different zones in welded structures has been analysed. Experimental facilities are under construction for this purpose. Release studies, as well as consideration of release-corrosion interaction effects, are also being undertaken as part of the IHCP activity on "Reliability of Medical Devices" in support of Directive 93/42/EEC. Moreover, a constant dialogue with Commission Services and industrial stakeholders is pursued to analyse normative R&D needs in the areas of low-level release from food packaging and other consumer goods.

Web Information resources

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

At the Food Products & Consumer Goods Unit Site:
Contact Materials: http://food.jrc.it/activities/contact/index.htm

Selected Publications


Genetically Modified Organisms

Biotechnology has become one of the most important scientific, technological and industrial sectors in Europe. In the fields of agriculture and food production, it holds the promise of increased productivity, improved systems for integrated pest management and the production of foods with a higher nutritional value. These developments, however, also raise concerns in various parts of society such as consumer groups (regarding the safety of GMO foods as well as ethical and social aspects) and environmental groups (in particular, in connection with perceived long-term consequences for the biosphere).

The European Commission has formulated a number of regulatory measures aimed at the preservation of the environment and at the protection of human and animal health. Important international trade issues related to biotechnology, especially in the context of the use of GMOs for food production, have also emerged over the last few years.

The work undertaken at the IHEC in connection with the project "Genetically Modified Organisms in Food and Environment", is aimed at providing scientific and technical support for the implementation of EU policy in the area of biotechnology. The project involves collaboration with the Commission's Environment DG, responsible for environmental legislation regarding biotechnology and the Health and Consumer Protection DG, responsible for food matters.

The activities on GMO releases into the environment include the establishment of a system for exchange of information related to experimental releases of GMOs. Other projects deal with the development and harmonization of risk assessment strategies and methodologies. In support of community legislation in the area of novel foods, analytical methods for GMO detection in food are being developed and validated. Finally, technical support is given to the Scientific Committee on Plants and the Scientific Committee on Food to prepare a number of working papers and contribute to evaluating data on genetically modified plants that have been submitted for marketing.

New scientific developments, appearing in the scientific literature, are evaluated with regard to their suitability for insertion into analytical techniques to detect specific genes in crops, foods and feed stuffs. Advance studies are also carried out on the uses and functions of new genetic traits for GMO development.

Within this research area, dissemination of information is ensured through network-based information services, which are to be further expanded during the Fifth Framework Programme. Established networks involving authorities and laboratories in Member States and a continuous interaction with Commission Directorates-General (mainly Health and Consumer Protection, Environment, Enterprise, Agriculture) ensure that political concerns, with a strong technology-driven component, are properly anticipated and addressed at the IHEC.

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Databases to administer the release of GMOs in the environment

Each time an intentional release of a GMO for R&D field trials is undertaken in an EU country, the competent national authorities evaluate and either approve or reject the notification dossiers submitted to them. The summary of all such dossiers — approved or not — must be made available to the other EU Member States. The European Commission has entrusted the IHCP with the task of setting up a system for the exchange and analysis of the information contained within these notification files. In 1999, more than 220 dossiers on R&D field trials were handled, including proof reading and conversion to a digital format (when necessary) before being distributed to Member States’ Authorities. Submission is made using the European Commission’s Electronic SNIF (Summary Notification Information Format) software, developed with the purpose of exchanging, in electronic format, the information between Competent Authorities of Member States and the European Commission. Up to the end of 1999, 1500 dossiers were received and distributed by the IHCP. Summaries (non confidential) can be consulted at the web site “GMOs - Food and Environment” (http://food.jrc.it/gmo/).

An important development, initiated in 1999, ensures the secure exchange over the internet of the full dossiers that are circulated to all Member States in the case of an application for the commercialization of a GMO. Also foreseen is the implementation of a network-based register of notifications/deliberated release of GMOs. This "Extranet", a prototype version of which was presented at the end of 1999, will link EU Member States and the Commission through a secure, access-controlled, information service and will allow rapid submission and distribution of the dossiers. It will also be a useful information tool for risk assessment.

A supplementary development of the "Extranet" will comprise the implementation of a reference database service on genetic modifications. Information on the sequences and gene constructs will support inspection processes, for which detection and identification are fundamental. The same information can also provide a scientific reference that can be used, for instance, in the development of appropriate GMO detection methods.

Analytical Methods

In order to ensure reliable composition monitoring of food items (including labelling compliance) there is a need for validating analytical methods that enable the detection, identification and quantification of GMOs in a given food product. These methods will also supply industries with quality control methods that can aid them in the labelling of food items and will provide enforcement laboratories with the tools necessary to carry out their analytical tasks.

A genetic modification can be revealed and quantified either by detecting the presence of a specific trait encoded within the DNA or by determining the synthesis of a new protein that is exclusively produced in the GMO and not in the traditional variety. The IHCP has considered both approaches in close collaboration with the Institute for Reference Materials and Measurements (IRMM), and has validated a number of detection methods in cooperation with a large number of laboratories in and outside the EU.

Detection of modified DNA is mostly based on the polymerase chain reaction (PCR). A PCR method allows the selective amplification of specific DNA sequences — it can generate millions of copies of DNA molecules in less than an hour. Therefore, PCR-approaches can potentially enable the detection of GMOs even when present in relatively small amounts. The IHCP was involved in a validation study, undertaken at European level, for the detection of GMO material in flour raw materials derived from modified crops (Roundup-Ready® soybeans and BT-176 maize). The results have demonstrated that the PCR-based method is a suitable screening technique for these specific flours derived from modified soybeans and maize, present in various concentrations at their non-GMO counterparts.

In addition, the validation of an enzyme linked immunosorbent assay (ELISA) method, highly specific for a protein present in herbicide tolerant GM-soybeans, was completed. The ELISA method is based on a specific interaction between proteins and their antibodies. The validation study carried out by IHCP involved a total of 38 laboratories from 13 countries and was designed to test if a sample contained either "at least 2% GM-soybeans" or "less than 2% soybeans".
As a competitive support to Health and Consumer Protection, the IHCP recently validated another PCR-based screening method for the detection of GMOs in processed food. Five different food matrices were prepared for this purpose (polenta, acidified soybeans, infant formula, and two types of biscuits), each containing a varying content of Roundup Ready® soybeans and BT-maize. The results demonstrated that this method was able to detect GMOs at all concentrations used in the preparations as mentioned above, despite the extreme physical stress (e.g. heating for 45 minutes at 100 °C or 10 min at 180 °C) applied to the food samples or the mixing of multiple components such as biscuit preparation and is sufficiently simple and allows reproducible analysis. However, extreme care should be taken to minimise the occurrence of false positive results.

Another method validation was based on a double quantitative PCR approach that allowed the quantification of the GMO content in a given sample in relation to the total amount of the plant species present in the composition of the processed food item. The results obtained in this study indicated that in specific cases a correct score of only approximately 75% could be achieved for all materials with varying GMO content (0.1 %, 1 %, 2 % and 5 %).

Activities in the area of analytical methods included a continual support to the development of reference materials, undertaken at the IRMM. Multiple batches of reference materials containing GMOs have been extensively analysed by direct PCR, nested PCR and the use of a large variety of PCR primers. In this way, the biological quality of the materials could be assessed and recommendations made on the requirements for the production of reference materials. The co-operation with IRMM will continue in order to establish adequate protocols for the production of additional batches of certified reference materials.

The activities on method development for the detection of GMOs will be further strengthened following the upgrade of the molecular biology laboratory currently underway to expand the range of research and development on molecular diagnostics methods. Intensive contacts with other research groups have been established in order to have access to the latest developments in analytical research. The IHCP was active in the organisation of training workshop concerning the detection of modified DNA, held in Parma in June 1999 and June 2000 (presentation of the results of the validation study, information on protein methods). The IHCP will also organise in its own laboratories at JRC Ispra, together with the World Health Organisation (WHO), a series of training courses for official control laboratories (especially those in Accession Member States and developing countries). The first courses will start in September 2000.

As a follow up to the requests from Member States authorities, the IHCP will co-ordinate the "European network on GMO laboratories" for which the kick-off meeting has taken place in June 2000 at the JRC Ispra. This network aims to act as a tool for facilitating and speeding up collection (e.g. data bases on gene sequences and analytical methods) and exchange of information, the coordination of tasks to reduce the escalation of costs, the identification and solution of technical gaps (e.g. in analytical methods and their interpretation) or needs such as reference material, sampling plans, and online access to shared expertise.

In addition, the IHCP was the organiser of several workshops on GMO detection methods (e.g. November 1999 in Ispra, December 2000 in Brussels in collaboration with the International Life Sciences Institute) and is actively participating in the CEN working group (TC 275/WG11) on GMOs.

Selected Publications


Web Information resources

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

At the Food Products & Consumer Goods Unit Site:  
Genetically Modified Organisms:  
http://food.jrc.it/activities/gmo/index.htm  
GMOs in Food and Environment:  
http://food.jrc.it/gmo/
The Validation of Alternative Biomedical Test Methods

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

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

This involves the development and evaluation of in vitro methods (cell and tissue cultures), and the use of computer modelling based on structure-activity relationships and physiological and biokinetic modelling. The approach is based on a mechanistic understanding of effects and responses at the molecular and cellular levels.

ECVAM has a wide network of collaborators in academic, industry and government laboratories in the Member States, Switzerland, the USA and Eastern Europe, and works with other EC Directorates General to secure the international acceptance and implementation of valid ways of providing better protection of human health, without causing animal suffering.

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The Validation Process

Because of the serious decisions that have to be taken about the potential effects of various kinds of chemicals and products, the validation of new methods requires a formal process, usually involving the blind testing of coded test items in a number of laboratories, with independent selection and coding of the test items, and independent collection and analysis of the test results. This part of the process is preceded by confirmation that a method has been satisfactorily developed to meet certain criteria, and a prevaled stage to assure that an optimised test protocol is available and can be transferred from one laboratory to another. It is followed by an independent evaluation of the outcome of the validation stage (e.g. by the ECVAM Scientific Advisory Committee [ESAC]), then consideration by the appropriate regulatory bodies in the Commission and the Member States.

Three non-animal test methods completed this process in June 2000, when their acceptance as Annex V guidelines in relation to the classification and labelling of dangerous chemicals (Directive 67/548/EEC) was published in the Official Journal of the European Communities. A number of other methods are approaching regulatory acceptance.

ECVAM has reached agreement with other EC Directo rates General, appropriate authorities in the Member States, the US Inter-Agency Coordinating Committee on the Validation of Alternative Methods (ICCVAM), and the OECD Secretariat, on the criteria for test development and acceptance. In addition, to facilitate the validation and acceptance of new tests methods, the principles of Good Laboratory Practice (GLP) have been adapted for application in in vitro toxicology by the participants in an ECVAM workshop. ECVAM has developed an on-line information system in the form of a set of integrated databases (gplOLIVtextCJRc), designed to facilitate the management of in vitro laboratories and validation studies according to GLP.

Metabolism and Neurotoxicity

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

During 1999, progress was achieved in the development of in vitro tests for detecting metabolism-related problem compounds, including the establishment of an in vitro co-culture approach involving genetically engineered cell lines expressing cytochrome P450 enzymes (catalysts for several metabolic-mediated toxicity processes) and human whole blood in order to study transcellular toxic effects to the immune system, and also with embryonic stem cells, to provide a metabolically competent alternative to in vivo assessment of toxic effects in the developing embryo (see the section on Embryotoxicity). This work has been conducted with partners in Germany, The Netherlands and the UK.

Another significant achievement in 1999, in the area of neurotoxicity, also with German partners, was the successful engineering of a neuronal cell line to provide an in vitro assessment model for toxic effects in brain cells. The model developed and prevalidated at the ECVAM laboratories provides a panel of cells with either increased or decreased sensitivity toward apoptosis.
(programmed cell death), an important indicator in the evaluation of toxicity to brain cells. Apoptosis is also involved in pathological mechanisms, e.g. Alzheimer’s disease, Parkinson’s disease and prior-related diseases.

3 [Image from TechnoFlash Winter – Neurotoxicity Evaluation]

The results indicate that this system, for which a patent has been filed, will be a relatively simple, quick, reliable and reproducible means of assessing the toxic effects of drugs and environmental compounds in neuronal cells, even down to very low levels of exposure. It will also provide a new approach for the screening of medicines, which either enhance apoptosis in cells in which apoptosis is normally inhibited, or inhibit it in cells in which apoptosis is abnormally higher.

Activities concerned with uptake across the intestinal barrier focused on the use of the CaCo-2 cell line, and involved collaboration with Glaxo-Wellcome (Verona) and with the Institute Superiore della Sanità (Rome). An ECVM workshop on in vitro models of the intestinal barrier was held in Rennes (France).

A very promising ECVM-sponsored study on prevalidation of in vitro models of the blood-brain barrier was under way in 1999, coordinated by Pharmacia & Upjohn AB (Stockholm).

A novel use of the Tcncomouse as an in vitro testing system that permit long-term chronic toxicity studies, has been transferred from the Central Science Laboratory (Norwich, UK). In this system, cells can be maintained for several weeks or months without subculturing. A pilot study initiated in 1999 involved a human cell line exposed to three compounds (3-nitropropanoic acid, cadmium chloride and paraquat). This system will also be used for metal toxicity studies.

An ECVM workshop on chronic repeat-dose toxicity testing in vitro was held in Innsbruck in 1999.

Haematotoxicity and Anti-cancer Drugs

The bone-marrow, a major part of the blood-forming system, is the target for a wide variety of industrial and, environmental chemicals, and damage to blood cell formation is a major side-effect of anticancer drugs. The availability of in vitro tests for evaluating the consequences of exposure to medicines or other chemical substances in the various blood-cell lineages would be a very significant development.

A formal validation study of the CFU-GM (colony forming unit - granulocyte/macrophage) assay for acute-onset neutropenia, sponsored by ECVM, was continued in 1999. It involves four laboratories in the EU (Italy, Belgium, Spain and France) and one laboratory in the USA, as well as a collaboration with the US Food & Drug Administration (FDA). This study is aimed at facilitating the pre-clinical assessment of anti-cancer drugs and the provision of a rational basis for clinical dosage estimations and for setting human exposure limits in clinical trials.

Advanced in vitro techniques are also being developed to monitor molecular toxicity indicators in haematopoietic cells, and immunocytotoxicological techniques are being used to evaluate the toxicity of new anticancer drugs to cancer cell lines. Additional work included an evaluation of the use of human bone-marrow cells and human cord blood cells as precursors for blood cell lineages for toxicological assays, leading to the successful development of a protocol for using cord blood as a source of cells for a CFU-MK (colony forming unit - megakaryocyte) assay. Studies on direct effects of drugs on erythroid cell progenitors in long-term bon
Embryotoxicity

The potential of chemicals and products to damage the developing embryo and fetus is a major problem in toxicology. A prevalidation/validation study of three in vitro embryotoxicity tests, coordinated by ZEBET (Berlin) for ECVAM has just been successfully completed. Two of the tests, the micromass assay and the whole rat embryo culture method, were conducted laboratories in Finland, France, The Netherlands, Switzerland and the UK. The third test, employing embryonic stem cells (ESC), involved German and Swiss partners and ECVAM's own laboratories. In this test, embryonic bodies are created in vitro, which are composed of beating cardiac cells, haematoepoietic cells, muscle cells or nerve cells. The ability of chemicals to affect the differentiation of cells derived from ESC along specific pathway can thus be evaluated.

Research at ECVAM is focused on the production of genetically ESC, in order to develop an effective high-throughput system, and on the development of more sophisticated endpoints to provide answers to mechanistically-relevant questions, such as cadmium and rhodium.

Metal Toxicity

Trace metals and their compounds play a crucial role in many biological systems, but the recognition that trace metals can also induce toxic, mutagenic and carcinogenic effects in humans is addressed by a number of EC Directives (80/778, 80/1107, 87/416, 89/458, 91/441), which define limits for the daily intake of trace metals present in the environment and for threshold limit values in the workplace. In addition, there is a growing interest in the use of trace metals in cosmetics, drug therapy, and in other medical applications, as in the case of biomedical devices.

The activities of ECVAM during 1999 included assessments of the toxic and carcinogenic effects of trace metals, and involved multiple collaborations and studies with external partners. These have resulted in a critical review of the use of rodent cell lines (BALB/3T3 and SHE cells) or human cells (immortalised and primary skin keratinocytes, HaCaT cells) for carcinogenic potential evaluations, and the use of the in vitro micronucleus test as a complementary method for the assessment of genotoxic effects in cell transformation assays. Experimental work covered the optimisation of the BALB/3T3 assay for cytotoxicity screening, and the concurrent assessment of morphological transformation, as a basis for inter-laboratory prevalidation studies. The screening of 47 metal compounds was carried out with this assay. Concurrent cytotoxicity/morphological transformation assessments were also made for organic/inorganic arsenic compounds, and salts of platinum, palladium and rhodium.

Studies have also been completed on the effects of inorganic arsenic and organo-arsenic species and on the screening for 20 metal compounds, and, in particular, platinum, palladium and rhodium compounds, on immortalised and primary skin keratinocytes (HaCaT cells). Additional studies in 1999 included the use of cadmium as a reference compound in the Tecnomouse system for studies on the long-term (chronic) effects of trace metals. The development of test methods to evaluate metal toxicity to the immune system, by using human lymphocytes/monocytes from healthy and atopic subjects, was also pursued.
**Biologicals**

Biologicals are products such as vaccines, immunoglobulins, hormones, monoclonal and polyclonal antibodies, and other related products. The quality control and safety testing of biologicals still require the use of large numbers of animals, even if advanced in vitro tests already exist for some of these purposes.

ECVAM sponsors, or is a partner in, a number of prevalidation and validation studies on methods for the quality control of immunobiologicals and hormones. It participated in a successful validation study on a serological test method for the potency testing of erysipelas vaccines, which was conducted by the Paul Ehrlich Institute (Germany). The final report for a study a serological procedure for the potency testing of human tetanus vaccines is under consideration. ECVAM has a working group on non-lethal endpoints, and a very welcome development is that the upcoming new edition of the European Pharmacopoeia will state that non-lethal endpoints for animals should be applied wherever possible. The ESAC has endorsed In vitro methods, now available for all levels of monoclonal antibody production, as a replacement for animal production systems, which can cause much suffering.

A joint AGAATT/ECVAM workshop on Three Rs approaches in the production and quality control of avian vaccines was held in 1999, and comments representing the conclusions of the workshop participants on the revised monographs for avian live vaccines have been sent to the European Pharmacopoeia.

Three studies under way in 1999 focused on the relevance of the target animal safety test, prevalidation of serological methods for the potency testing of bacterial vaccines, and prevalidation of physico-chemical methods for the potency testing of recFSH (recombinant follicle stimulating hormone).

**Computer Modelling**

Computer-based systems for predicting toxic effects are of increasing value and significance. For example, structure-activity relationships (SAR) have been derived to predict the potential of chemicals to cause skin corrosion, eye irritancy and acute neurotoxicity, and the potential of pharmaceuticals to cause carcinogenicity. A novel quantitative SAR (QSAR) method for generating elliptic models of toxicity has been developed and published.

A tiered testing approach to hazard identification has been evaluated by using the endpoints employed in skin corrosion and eye irritation testing. The findings were communicated to the OECD Secretariat when the OECD was considering proposed tiered testing strategies for these endpoints. The OECD testing strategies have now been adopted.

Additional work has focused on the development of a bootstrap resampling method for comparing the predictive abilities of different classification-based models.

**The tiered approach to hazard classification**

<table>
<thead>
<tr>
<th>OECD strategies for acute eye and skin toxicity</th>
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<tr>
<td>Existing knowledge</td>
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<td>Chemical structure</td>
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<td>Physicochemical method</td>
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<td>Animal test(s)</td>
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</table>

**Biostatistics and Study Design**

The highest possible standards of experimental design, and independent data retrieval and analysis, are crucial to ECVAM’s work as a recognised validation agency. ECVAM’s statistician therefore plays an important role in advising on prevalidation and validation study design, as well as providing unbiased reports on study outcomes and conclusions.

**The ECVAM Scientific Information Service (SIS)**

In 1996, ECVAM established a unique scientific information service (SIS), in line with the JRC commitment to the dissemination of information on advanced alternative methods. ECVAM-SIS consists of factual and evaluated information on advanced non-animal methods for toxicology assessment. It provides full method descriptions, including their development and validation status. Furthermore, detailed protocols for their use, test compounds to which they have been applied, and test results, information on user laboratories, and details on formal validation studies, are made available.

1999 saw the completion of the establishment of the main SIS databases. These included the Alternative Methods sector (dbAlm) with the inclusion of INVITOX protocols (transferred from FRAME in the UK) in their entire layout, the core application of the Validation Studies (dbVs) sector, and the Bibliographic References sector, with ECVAM workshop and task force reports. Refinements of the Data Entry Module for data collection were also concluded, as well as the completion of pilot studies for data collection on nine priority topics.
for non-animal toxicity testing. Systematic data collection for seven topics related to toxicity testing of chemicals and/or formulations was initiated, and its completion is expected in 2001.

A publicly available on-line version of ECVAM-SIS is soon to be made available on the World Wide Web (http://ecvam-sis.jrc.it). Public access will be provided for selected SIS data sectors, and the present SIS Internet version will be refined and completed with an additional sector.

The definition of the first thesaurus (systematically ordered vocabulary) on alternatives in the area of toxicity testing will be concluded in 2000, with the active collaboration of Dr Stuart Nelson (US National Library of Medicine, [NLM]), the world’s leading authority on thesauri. ECVAM-SIS has been invited to participate in a newly formed ad hoc group of the NLM, to address the question of establishing better information retrieval on alternatives in literature databases.

**Special Event**

ECVAM organised the 3rd World Congress on Alternatives and Animal Use in the Life Sciences, held in Bologna, Italy, from 29 August to 2 September 1999. This was a major event, which gathered about 800 scientists, including 30 from the JRC, and will certainly reinforce the reputation of ECVAM, the IHCP and the JRC in the biosciences.

The main themes were:
- the development of replacement alternatives;
- the validation and regulatory acceptance of alternative tests;
- reduction alternatives;
- the refinement of animal procedures; and
- education, ethics and databases;

Eight plenary and special lectures were held, with 35 symposium sessions on these five themes. There were also 30 workshops and point/counterpoint sessions, more than 200 poster presentations, and an exhibition of commercial presentations and displays by organisations devoted to animal welfare and alternatives. Special discussions were held on a number of controversial issues, such as whether conflicts between human rights and animal rights are inevitable, whether the use of non-human primates in laboratories could (and should) be phased out, what needs to be done so that vaccines can be produced without using animals, and how human tissues can be safely and ethically obtained for use in research and testing.

The 1800-pages Congress proceedings will be published by Elsevier BV, Amsterdam, The Netherlands, in September 2000.

The highlight of the Congress was the acceptance, with acclamation, in the Aula Magna of the University of Bologna, Europe’s oldest university, of a Declaration of Bologna, endorsing the Three Rs (reduction, refinement, replacement) of Russell and Burch, as the most humane and ethically acceptable way of protecting both animal welfare and the legitimate interests of science and industry.
Selected Publications


BALLS, M. - The Precautionary Principle should be Used with Caution and Should be Applied to Animal Experimentation and Genetic Manipulations, not Merely to Protection of the Environment (Editorial). ATLA, Vol. 27 (1999) 1-5 - ART 45665


Web Information resources

At IHCP site:
http://ihcp.pcu/thelIHD/Activities/ACTVal.html

ECVAM - Scientific Information Services (SIS)
http://ecvam-sis.coc.eu.int
Biomedical Devices and Functional Systems for medical applications.

An increased average life expectancy implies that critical body parts, e.g., bones, joints, will wear out and must be replaced. Biomedical devices or implants, engineered from biomaterials, and designed to perform specific functions now play a major role in replacing or improving the function of every major body system (skelatal, circulatory, nervous, etc.) and include dental implants or orthopaedic devices such as total knee and hip joint replacements, spinal implants or bone fixtures. In the next few years, the forecast rate of joint implantation in Europe is 400,000 hips/year and 100,000 knees/year, with the number of younger patients steadily increasing. Failure (e.g., fracture) of prosthetic devices during use exposes patients to serious risks, in particular, when replacement surgery must be carried out. Moreover, for younger patients, acceptable performance of these devices should be maintained for long periods, to minimize the number of replacement surgery. For replacements, longer surgery times and extended hospital stays as well as extended recovery and rehabilitation are required, which lead to an increase of costs. From a regulatory point of view, acceptance of a wide range of medical devices at an European level, requires the validation and harmonization of testing and characterization methods for the systems and the materials used. While in Europe, the use of biomedical materials and devices must comply with CEN standards (Directive 93/42 EEC on medical devices), it is perceived that these standards are unsatisfactory. Providing Commission services (DG Enterprise, DG Health and Consumer Protection DG or CEN) with scientific and technical information related to the improvement of standards is necessary and is the basis of the projects Reliability of Biomedical Devices (REMED) and Functional Systems for Health and Consumer Protection (FUNSYS) of the #HCP.

These projects rely on existing NCP competencies in materials science, materials testing and analysis techniques and are widened by an interdisciplinary cooperation (including networking and other collaborations with Universities and industry) between engineers, physicists, chemists, biologists and physicians. It covers four main lines: Surface Modification, Performance Testing, Lifetime Assessment and Modelling and Characterization techniques. Surfaces are crucial for biocompatibility; i.e., surface modification and the processing/use of coatings must be validated to establish the best procedures to be adopted for surgical tools, prosthetic devices or other biomedical implants. Performance testing under realistic load spectra and body environmental conditions must be refined for normative purposes, which include the identification of relevant test parameters to characterize the response of various biomedical devices in practical applications on which standardization can be based. Performance testing also delivers relevant data for lifetime assessment and risk assessments of premature failure, which guarantee transferability of results to a sufficiently wide range of applications. In support to the above activities, careful selection and assessment of characterization techniques is necessary. These are aimed to satisfy all the program lines and by determining the material properties relevant for the specific applications to endorse quality assurance and lifetime assessment procedures.

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Performance Testing

Testing of implants in conditions that simulate the specific clinical use (e.g., under realistic dynamic loads, or in presence of biological fluids during prolonged time periods) is a key issue to validate lifetime assessment models and ultimately to endorse the reliable use of biomedical devices. Pre-normative test development is needed to identify and evaluate the relevant parameters to be considered by regulators and industry for standardisation and also to allow the qualification of new developments in the field such as the use of new materials, including coatings. An additional requirement, is becoming more and more important: the need to foresee that the long-term integrity of the implants during long-time use is insured, e.g. taking into account potentially harmful material release, likely to cause toxic effects in the human body. This demands the design of performance tests for biomedical devices with increasingly sensitive test methods.

In support of the Directive 93/42/EEC pre-normative testing for hip and knee implants was undertaken at the IHCP. Current methods and testing parameters were critically reviewed. The performance of these implants is strongly related to the behaviour of the implants, which should emulate the characteristic (and rather complex) motions and frictions occurring in the body. Wear and corrosion phenomena are most likely to occur at these joints, with consequent releases of material into the biological tissue environment. Development of pre-normative testing methods, including the effect of different biological lubricants on wear and corrosion has been pursued during 1999. To support these activities, a hip joint simulator with a biaxial-axis dynamic loading has been developed and constructed. A twelve-station screening wear test facility, featuring a multi-directional sliding motion is also under construction. These facilities allow clinically relevant evaluation of candidate materials to be used in artificial joint replacements.

Further, to expand the technical capabilities (long term testing, testing of different medical implants) at the IHCP, multi-station hip and knee joint simulators will be set-up that will enable the laboratory to carry out a wide range of reference tasks, at European level, in the performance assessment of biomedical implants. For on-line monitoring of small amounts of materials released due to wear, Thin Layer Activation (TLA) was employed. For the TLA technique, high-energycharged particle beams, available at the IHCP Cyclotron, are used to create radiotracer unstable isotopes that emit specific radiation such as gamma rays - in a thin surface layer of a material. Any loss of activated material due to wear results in a decrease in gamma activity of the activated component. This decrease is giving a very sensitive measure of material release. These studies also included application of TLA approaches to medical grade polymers. Upgrading of the related facilities will be finalized in early 2000.

Due to the increasing use of surface treatments in medical implants, some surface modified systems were included in wear testing and electrochemical characterisation. The latter was used for aluminium oxide layers formed by thermal oxidation treatments. The potential use of surface treatments for medical implants will be further explored within a competitive activity to be initiated in early 2000. This project, named "Development of Alumina forming ODS Ferritic Superalloys as new biomaterials for surgical Implants" (ALUSI) involves seven partners from three European Countries and aims to develop hip and knee implants with a long life expectancy.

Studies on chemical release from medical implant materials, including orthodontic materials are driven by the need to supply measurement methods for qualifying the risks related existing and new materials used in medical devices. In this frame, the set-up of a dedicated laboratory was undertaken, including the purchase of electrochemical facilities. These will allow an examination of the reliability of chemical release testing methods currently in use and the definition of more realistic testing environments (e.g., test solution, time period, test volume) and procedures to simulate the level of releases from medical implants and material, and to be applied on measurements of potentially dangerous elements or ionic species (e.g., Cr6+). Experimental activities in 1999 covered the problem of experimental artefacts related to conventional migration cells. A new concept to overcome this is presently under development. Development of radiotracer reference methodologies able to measure low level release in simulated biological environments was also initiated. This considers the integration of TLA and measurement of the associated radiotracer concentrations in the testing methodologies. The preliminary results, obtained in 1999, indicate that the achieved detection limits are sufficiently low, even in complex biological environments. Thus the method
can be of great value as a reference for the validation of conventional (chemical) methods.

TLA Facility

**Biomechanical Modelling and Lifetime assessment methods**

Work undertaken in 1999 has focused on dental applications. Bioreabsorbable membranes, new titanium alloy (titanium, zirconium and niobium) and BICON® dental implants have been considered for mechanical modelling. The bioreabsorbable membranes were obtained by blending of gellan and polivinilic alcohol. Tensile tests to characterise the mechanical resistance as a function of the chemical composition have been conducted.

In order to understand the behaviour of a special type of implant in contact with the cortical bone, BICON® dental implants have been characterized through mechanical compression tests and modelling studies (Finite Element Modelling using ABAQUS and FEMAP codes), simulating dental implants under masticatory loads. For this purpose, the dental implant was embedded in an acrylic resin, whose elastic properties are similar to those of the cortical bone. Different abutment orientations, between the main axis of the implant and the cortical bone, have been considered. Maximum allowable loads for this system, before the onset of plastic deformation, were determined, evidencing that the strength of the implant-abutment joint is sufficient to withstand the maximum expected stresses. Further, these results allowed adjusting the parameters in the modelling FEM code used to calculate the stress distribution in the system. This information will be used as an input to model the implant response under (more representative) alternating loads, and the evaluation of the lifetime of the system dental implant/bone.

Finite element modelling (ABAQUS and FEMAP codes) was also used done to study the mechanical behaviour of bio-absorbable membranes. Such membranes are used in the regions surrounding a tooth (periodontal) to coat defects related to the main progressive degradation mechanism of the tooth anchorage in the mouth cavity (parodontopathy). The studies aimed at the estimation of the stresses and deformations occurring in membranes, composed of Gellan and Poli-Vinil-Alcool [PVA]. Tensile tests were conducted to determine the module of elasticity (E) of membranes and the mechanical resistance for samples with distinct percentages of Gellan and Poli-Vinil-Alcool [PVA], characteristic compounds of the bio-absorbable membranes. For a given stress applied, samples with compositions from 20% to 100% of Gellan, evidence different deformation states of the membrane. Consequently, membranes with different composition can be selected to address different periodontal pathologies.

As regards new titanium alloy two lines have been followed in 1999. The first focused on the chemical and metallurgical characterisation, studying the effect of thermal treatment on the crystalline structure. All chemical and metallurgical characterisation has been conducted by means of SEM, X-ray, optical microscopy and Vickers micro hardness measurements. A second study focused on the characterisation of the mechanical behaviour of the alloy under tensile testing. These experiments are to be complemented by FE-simulations in order to improve the understanding of the mechanical behaviour after different thermal treatments.

A feasibility study was done for the establishment of a register for prosthetic devices and surgical techniques. It lead to the submission of a Thematic Network proposal "European Arthroplasty Register (EAR)" with 15 partners from 10 countries. The main scope is to collect data on surgery and follow-up of implants from the pre- and post-operative situation and to set up a data bank, allowing a statistical analysis of the performance of different types of prosthesis and surgical techniques. The EAR shall foster an improved tractability of orthopaedic implants and the creation of protocols for clinical research as part of a medical quality system. EAR shall provide basic information and conceptual guidance for a European Retrieval Register whose establishment is envisaged at a later stage.
The development of new materials and processing methods has led to an increased interest in advanced functional devices for biomedical applications and consumer protection. Examples in the biomedical field include sensors for mechanical strain, temperature, heart function, blood flow, and biochemical sensors for monitoring of levels of glucose and urea, filters for entrapment of blood clots in critical blood vessels, bone suture material, dental arches, steerable catheters, stents and micro electro-mechanical systems (MEMS). Examples in the consumer protection field include sensors for online control of contamination and atmospheric impurity, sensors/biosensors for food degradation monitoring. There is a continuous need for development and validation of characterisation and performance testing methods for qualification and quality control and for modelling of either individual components or of entire multicomponent for assessing reliability and potential failure mechanisms. This project is particularly oriented towards monitoring and assessing new and emerging technologies. Specific experimental programmes utilising existing competence and facilities will be used. In the first year, the studies were concentrated on rather broad surveys of potential areas of interest such as shape memory alloys, and micro-electromechanical system (MEMS) materials.

Smart materials – shape memory or superelastic devices have the potential for a number of applications (e.g. orthodontic devices, bone remodelling and repair devices, surgical instruments). In 1999, experimental work has been initiated on deposition of shape memory thin films. The method of co-sputtering was employed, but this proved too inhomogeneous a process for good repeatability. Thus appropriate sputter targets and pure Cu rods with which to dope the films will be considered for future experiments.

Glancing angle XRD patterns of (a) NiTi co-deposited at room temperature, and (b) deposited from a NiTi target at 360°C. The latter shows a nanocrystalline rather than an amorphous structure.
Participation in a shared-cost action (INDICOAT) on the use of nanoindentation for mechanical testing of thin films has facilitated an important increase in competence in this field. This field is highly important in testing and validating surface modified materials, and is potentially of great importance in mechanical characterization of MEMS components. A new X-ray based technique for density measurements of thin films and modified surfaces has been developed, for which a patent has been filed. For the subtask on "functionalisation of surfaces", the deposition equipment for carbon coatings has been installed and work will be initiated on carbon deposition onto shape memory wires in the first half of 2000.

Web Information resources

At IHCP site: http://ihcp.jicr.it/TheIHCP/Activities/ACTReh.html

Selected Publications


Medical Imaging Using Radiotracers

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

In recent years, more and more attention has been directed to the use of radioactive isotopes for therapy, especially for cancer treatment. The prerequisites for such radionuclide therapy are (i) the availability of a biomolecule with high specific uptake in tumour tissue and (ii) the availability of an appropriate radioactive isotope which can deliver a high radioactive dose to a very small area. In this way the biomolecule targets the tumour tissue and the decay of the radionuclide kills the tumour cells while preserving healthy adjacent tissue. Radionuclide therapy requires careful planning and monitoring of progress for instance by Positron Emission Tomography.

The enormous potential of PET in clinical practice and medical research as well as emerging radionuclide therapies for dispersed and inoperable cancers will lead to a strongly increasing demand for radiopharmaceuticals. An increased cost-effectiveness for example in the management of cancer patients and the medical and economic advantages of less invasive treatment of several groups of diseases will promote this development.

The Biomedical Devices and Systems (BMD) Unit has initiated activities in these areas in the 5th Framework Programme under the work programme Medical Imaging and Therapy using Radiotracers (MITRA). The MITRA programmes encompasses several tasks, including the production of medical radionuclides, support for their use in cancer therapies, and the validation of methods applied in medical imaging.

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

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In the 5th Framework Programme, the expertise and activities of the IHCP will be exploited to catalyze a joint European effort to assess the use of PET in oncology. The impact of its superior diagnostic sensitivity on health care systems, in terms of avoided surgery, early and less invasive treatments and reduced costs in the management of cancer patients will be analyzed. Such a health technology assessment shall provide important information on the economic and medical benefits of PET, which is required for its implementation in public health care systems by health policy.

**Production of Radioisotopes for Medical Diagnosis and Therapy**

Production of radioisotopes is carried out at the IHCP in order to increase the availability of several radioisotopes for medical research on synthesis and application of new diagnostic and therapeutic radiopharmaceuticals. Moreover, the IHCP contributes to satisfying routine needs in nuclear medicine by the foreseen commercial production of FDG (2-deoxy-2[18F]-fluoro-D-glucose) and by the established production of 123I for diagnostic purposes.

The production of radioisotopes for research is performed in collaboration with universities, hospitals and other research centers, for instance on the application of astatine-211 (211At) in cancer therapy. In this case the technical expertise of the IHCP in the field of target development is exploited in order to support new medical developments. The commercial production aims at the acquisition of practical knowledge in the field of quality control in all stages of production and on the technical issues of the distribution and delivery of short-lived radioisotopes to hospitals and research organizations. Such knowledge is of strategic importance, given the lack of Europe-wide regulations for the production and distribution of PET radiopharmaceuticals, which hinders the development of a common market and the distribution of PET facilities in clinical centers without their own cyclotrons. Such technical issues have to be considered properly for future European regulations on radiopharmaceuticals. For this purpose, contacts have been established with the European Agency for the Evaluation of Medicinal Products (EMEA) in order to clarify the legal aspects for the production and distribution of radiopharmaceuticals.

The production of 123I for diagnostic purposes has been continued at the IHCP cyclotron in 1999 as a third party work. One beam line has been upgraded in 1999 in order to enable the installation of the target and the production module for FDG (2-deoxy-2[18F]-fluoro-D-glucose).

A series of seminars on technical and tracer kinetic problems of PET was organized in collaboration with the PET center of the San Raffaele Hospital in Milan in the first half of 1999. These seminars covered relevant topics in PET data acquisition, imaging and radio-tracer production as well as the different application fields of PET in oncology, cardiology, neurology, psychiatry and drug development.

In the field of radioisotopes for therapy, efforts were focused in 1999 on astatine-211 (211At). The use of practically pure alpha-emitters such as 211At offers advantages in the treatment of dispersed cancers and micrometastasis by radionuclide therapy, since a high radioactive dose can be administered in a small area of only a few cell diameters. The IHCP reviewed the current state of the art in 211At-production technologies and organized and hosted a meeting with about 40 participants from 9 European countries. In the meeting it was agreed to collaborate and to establish a cyclotron network in order to increase the availability of this short-lived radioisotope. The IHCP cyclotron will play an important part in this strategy.

**Modeling, Image Analysis and Data Handling**

The use of laser light enables morphological and functional imaging 'in vitro' as well as non-invasive or minimally invasive therapeutic techniques. The work in 1999 concentrated on the establishment of a partnership leading to a European Thematic Network dealing with 'Optical Methods for Medical Diagnosis and Monitoring of Diseases' which has been submitted under the programme line "Quality of Life and Management of Living Resources" of the 5th EU Framework Programme. Mathematical methods which had been developed at the JRC in the context of studies on reactor safety, radiation shielding and light transport in air-water systems have been reviewed and work has been started on the conversion of existing computer codes for the description of light propagation in biological tissue. This nuclear spin-off allows the improvement of computer models for the optical characterization of biological tissue based on Monte Carlo Simulations and Diffusion Theory, implemented by finite element methods.
As an integral part of UTS development a comparative analysis tool for the so-called Medicine Analysis Network for Europe (MINE 1) is being designed and a prototype developed in collaboration with EMEA and the Heads of Agency Group. MINE 1 is a central database service that collects all the scientific efficacy and safety information in connection with medicinal products marketed in Europe. In 1999, the Products, Specialities and Presentation (PSP) data models and user access models for MINE 1 were designed and implemented. A medicinal products database model to manage data on authorised products was also established, containing structured information on medicinal products linked to the Summaries of Product Characteristics (SPCs). The redesign of EMR to comply with MINE1 database specifications was also undertaken, as well as the development of software tools enabling automatic transfer of ATS or SIAMED data to MINE1. This allowed the presentation, by the end of 1999, of a prototype version of MINE1 to interested stakeholders. The prototype already includes the available authorised medicinal products and their respective SPCs. It allows basic product searching, SPC retrieval and comparative analysis functions. It has two user interfaces: web and client server. A first demonstration of MINE1 took place at EMEA in London on October 1999 before the general demonstration, organized by EMEA in December 1999.

EudraNet 2 Network Services

UTS and MINE services are to be implemented on top of a new generation of network services for the Eudranet platform, developed by the JRC during 4th Framework Programme (referred as EudraNet 2). This evolution will take into account the requirements in terms of new family of services emerging from the enlargement of the platform to Central Eastern European Countries (CEEC), pharmaceutical industry and health professional and including new technological solutions, while ensuring secure access to information on safety and efficacy for consumers. The activities on EudraNet 2 in 1999 covered the implementation of a Virtual Private Network (VPN) on the internet. The integration of Public Key Infrastructure (PKI) pilot services was also pursued to address secure access and user authentication issues. The available communication channels with the EudraNet Working Group have permitted the production of proper specifications for EudraNet 2 acquiring the input of the customers.

The role of EudraNet 2 with respect to the ongoing activity as supported by the IDA (Interchange of Data between Administrations) Programme (TESTA 1 and TESTA 2) has been analysed and clarified with DG ENTERPRISE the leading customer of the project.

Selected Publications


Web Information resources

At JHCP site:
http://jcp.jrc.it/TheJHCP/Activities/ACTPharm.html
Consumer Protection on Electronic Commerce

In the next years, network enabled business practices, such as electronic commerce and other financial services/transactions, will become a growing medium for the interaction between consumers and sellers/suppliers. These activities will require a significant regulatory activity to protect both consumers and businesses and guarantee the development of eCommerce and eBusiness.

Consumer concerns regarding the use of presently available network services, such as electronic commerce can arise from different sources: limited understanding of procedures in the new media, poor awareness of their own rights, fears of disclosure (e.g., third party access to sensitive data, manipulation of contents of transmitted data, mistrust of the receiver regarding the authenticity of the sender).

Further emerging issues in this field will be related to the reliability of micro-payment systems as well as other banking/financial transaction services that will become progressively available on-line.

In the IMCP, the LEPEC (Laboratory for the Study, Experimental Testing and Monitoring of Electronic Payment & Electronic Commerce) project was established to identify, draw-up and refine strategic specifications and solutions, on a sound scientific/technical basis, aimed to provide tutelage of the consumer. LEPEC will be complemented by proactive actions to improve consumer awareness and to contribute to a more logical and secure development of network-enabled business practices. Important outcomes of these activities, which will be available to consumer associations or individuals as well as regulatory authorities and private companies, are:

- Evaluation reports on present and emerging electronic payment/transaction procedures and systems, underpinned by research studies on cryptography/crypto-security, with particular regard to the reliable and the secure use of these systems/services by the consumers.
- Systematic identification and classification of complaints (consumer-oriented, communication, technical).
- Evaluation criteria for the interoperability of electronic payment procedures and communication systems.
Payments and Transactions: Present and Emerging Electronic Systems

In this work area, activities carried out in 1999 were intended to survey the payment and transaction methods presently available via electronic communication networks, considering the protection of consumers economic interests. Specifically, a study on the security of on-line payments by credit card was undertaken. Two reports have been delivered on "On-line payments using credit cards: security and consumer protection issues" (March 1999) and on the "State of the art in cryptographic algorithms and protocols used for Internet security" (August 1999).

In the experimental area, the set-up of the LEPEC laboratory was initiated during 1999. This laboratory will be equipped with a complete computer installation, including specifically developed hardware systems and software tools to permit experimental evaluation of security systems and testing of particular payment methods. This facility will allow experimental corroboration of cryptography-based techniques that are fundamental building blocks for the security of electronic commerce and also enable research into biometrics and other identification systems designed to ensure that users' information is not disclosed. For this purpose, design of the Information Technology (IT) architecture for the LEPEC laboratory was carried out and selection of the Public Key Infrastructure (PKI) environment was also made.

Complaints Management System

The development of the Consumer Complaint Management System (CMS) was intended to allow the collection and analysis of consumer complaints on electronic payment and commerce occurring through networks and computer based systems. This will enable the determination of the most important consumer issues raised by electronic payments and electronic commerce and provide qualified support to EU consumer protection policies for electronic commerce and electronic payment systems. In 1999, the analysis and functional specifications for CMS have been carried out. In practice, CMS is designed to act as a communication tool between consumers and professionals and between businesses to handle complaints arising during transactions. Reports issued during the above period covered various topics, such as functional specification for a complaint management system; design of a prototype version of CMS; legal aspects underlying CMS and a detailed design of CMS. A prototype version of CMS was presented in November 1999 to the former DG XXIV. This includes a number of services such as collection, organisation and analysis of consumer complaints. A first workshop on LEPEC was hosted by the IHCP in November 1999 and the SPR staff assigned to LEPEC were involved in the preparation of a document "Electronic Commerce: JRC Strategy", in the framework of the JRC cluster on Electronic Commerce.

Following the JRC internal re-organisation it is planned to move the LEPEC activity to the Institute Systems, Informatics and Safety (ISIS) institute of the JRC during the year 2000. This is in order to concentrate all actions on reliability and confidence in electronic commerce within a single R&D group. The SPR Unit will complete its ongoing open activities and begin to the planned project transfer during May 2000.

Selected Publications

RANA, A. - ICH M2 Secure Email Interoperability Test - S/P/99.202
RANA, A. - Secure Email Interoperability Test - S/P/99.203
RANA, A. - Note on the Certification in Public Key Cryptosystems - S/P/99.204
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Chemical Substances:
Risk Assessment

The European Chemicals Bureau (ECB), through the "Chemical Substances: Risk Assessment" work programme of the ICPE provides scientific and technical support for the conception, development, implementation and monitoring of EU policies on dangerous chemicals. The ECB is the focal point for collecting information on new and existing chemicals; it manages the assessment of risks posed to workers, consumers and the environment. It supports legal classification and labelling, the notification of new substances, information exchange on import and export of dangerous substances, the development and harmonization of testing methods and the authorization of biocides. These activities include hazard and risk assessment, according to harmonized approaches to ensure the same level of safety everywhere in Europe.

Based on the conclusions of the Environment Council 24/25 June 1999, a new chemicals policy for chemicals will be established for the EU. The ECB will play an important role within the new policy since the Council asked the Commission to "ensure that the high quality of work carried out by the ECB will be maintained and reinforced".
**Existing Chemicals**

The Existing Chemicals Work Area of the ECB is responsible for the scientific and technical support to Council Regulation (EEC) 793/93 regarding the first three steps of the Regulation, i.e., the data collection, priority setting and risk assessment.

**Data Collection**

The EU Regulation was initially concerned with the so-called High Production Volume Chemicals (HPVCs). HPVCs are those substances, which are imported or produced in quantities exceeding 1000 tonnes per year and produced/imported between March 23, 1990 and March 23, 1994, covered by data collection phases I and II of the Regulation. In phase III of the data collection, companies which produce or import substances in quantities between 10 and 1000 tonnes per year (Low Production Volume Substances or LPVCs) were required to submit a reduced data-set by June 4, 1998. All data have to be submitted in a specific electronic format - Harmonised Electronic DataSET (HEDSET) - and are managed by the International Uniform Chemical Database (IUCLID), both developed and maintained by ECB. Furthermore, all companies that have submitted a data-set in any of the three data collection phases are required to update the information at least once every three years.

**Priority Setting**

Regulations state that the Commission, in consultation with the Member States, will regularly draw up lists of priority substances, taking into account their potential effects to man or the environment. The Commission and Member States utilise the collected information as a basis for selecting priority substances. Since 1994, three such priority lists have been published, referred to technically as the first, second and third priority lists.

**Risk Assessment**

Substances on the priority lists must undergo an in-depth risk assessment covering the risks posed to man (including workers, consumers and exposure via the environment) and the environment (including the terrestrial, aquatic and atmospheric eco-systems and accumulation through the food chain). This risk assessment follows the framework set out in Commission Regulation (EC) 1488/94 and implemented in the detailed Technical Guidance Documents (TGD) on Risk Assessment for New and Existing Substances. The first draft of the risk assessment reports are written by the Member States, which act as "rapporteurs". The Commission mediates the meetings, which attempt to reach consensus on the conclusions regarding the risk assessment. After adoption of the risk assessment, three publications are produced:

1. Comprehensive risk assessment report (as a book, on the ECB homepages and in the International Uniform Chemical Database (IUCLID))
2. Summary thereof (as an EUR report and on the ECB homepages)
3. Listing of the conclusions in the Official Journal of the European Communities.

The International Uniform Chemical Information Database (IUCLID), which is maintained and developed by the ECB, has been adopted as the standard database by the International Council of Chemical Associations (ICCA). This is a major step forward in standardisation, as the World Chemical Industry will now use the IUCLID
database to collect and distribute data on chemicals. This will have, as a direct consequence, an increase in accessibility of data on chemicals to the authorities, the Commission and the General Public and represents a substantial contribution towards meeting the objectives of the UNCEQ conference.

3. Image EUSES_EX
In the area of risk assessment, the ECB, in co-operation with MSS and OSPAR, has contributed to the elaboration of a framework for the development of a risk assessment methodology for the marine environment.

The work on the Existing Chemicals area resulted in a number of achievements in 1999.

- Receipt of three risk assessment reports from rapporteurs for discussion at EU level.
- Completion, at a technical level, of the 4th priority list and the EU working list.
- Compilation of areas of the risk assessment Technical Guidance Documents needing revision.
- Finalisation of the design work for the new version of IUCLID, referred as IUCLID 2.0 EC-B (Existing Chemicals - Biocides).

New Substances
Activities regarding new substances are carried out to fulfill the technical and scientific obligations of the EC regarding the notification schemes and risk assessment for all new chemicals that are made available in the EU as laid down in Directive 67/548/EEC, including procedures for risk assessment as laid out in Directive 93/67/EEC.

In 1999, 432 summary notification dossiers, 309 updates and 302 final classification and labelling proposals were received. These were loaded into the New Chemicals Database, checked and circulated to Member States and Norway. The European List of New Chemical Substances was updated (5th ELINC publication). The group co-ordinated upgrading of the Data Entry Screen (DES) software, used for preparation of notification dossiers. Numerous questions from Competent Authorities, Commission services and industry were answered. In 1999, two meetings with all Competent Authorities was held. The principal agenda items included notification requirements, testing strategies and risk assessment.

Biocides
To be implemented as a table List of biocidal substances, as defined in the European Directive

- Human Hygiene Biocidal Products
- Private area and public health area disinfectants and other biocidal products
- Veterinary hygiene biocidal products
- Food and feed area disinfectants
- Drinking area disinfectants
- In-can disinfectants
- Film preservatives
- Wood preservatives
- Fibre, leather, rubber and polymerised materials preservatives
- Masonry preservatives
- Preservatives for liquid cooling and processing systems
- Stimmicides
- Metalworking-fluid preservatives
- Rodenticides
- Avicides
- Molluscicides
- Piscicides
- Insecticides, acaricides and products to control other arthropods
- Repellents and attractants
- Preservatives for food or feedstock
- Antifouling products
- Embalming and taxidermist fluids
- Control of other vertebrates

Of the approximately 2050 substances, 540 are potential basic substances, i.e. substances which have a major use that is not biocidal and only a minor biocidal use and therefore unlikely to be of immediate concern.

The directive for 'placing on the market of biocidal products' was adopted by the European Parliament and Council in February 1998 and came into force on 14 May 1998. The recent adoption of the Directive means that the work in 1999 was oriented towards preparation for the start of the Review Programme of existing biocidal substances, which will be initiated in 2002.

Part of the initial work for the implementation of this Directive is to prepare and adopt technical notes for guidance (TGDs). During 1999, the Biocides work area held a series of meetings of expert working groups to examine the documents as a whole. The four expert working groups are Toxicology, Ecotoxicology, Fate and Behavior in the Environment and general issues. Work has been done to finalize the guidance document
The IHCP, through the Export/Import area of ECB, was involved in 1999 in the preparation of National Chemicals Management Profiles in the EU. A National Profile provides a comprehensive overview and assessment of the existing national legal, institutional, administrative and technical infrastructure related to the management of chemicals, and has been established by the United Nations Institute for Training and Research (UNITAR) under the programmes on chemicals and waste management. These national profiles are available on the Internet.

The EDEXIM (European Database of EXport and IMport of certain dangerous chemicals) database, developed and maintained by ECB, is a uniform system, which includes an electronic transfer facility to register import/export of restricted chemicals under Regulation (EEC) 2455/92. The database is available on the internet both as a public version – supplying useful information to Industry and to non-EU countries – and a Member State version that supports the implementation of the provisions set out in the EU regulation.

**Web Information resources**

**At IHCP site:**

http://ihcp.jrc.it/TheIHCP/Activities/ACTChem.html

**At the European Chemicals Bureau site:**

Home Page: http://ecb.jrc.it/
Existing Chemicals: http://ecb.jrc.it/existing-chemicals/
New Substances: http://ecb.jrc.it/new-chemicals/
Biocides: http://ecb.jrc.it/biocides/
Classification and Labelling: http://ecb.jrc.it/classification-labelling/
Testing methods: http://ecb.jrc.it/testing-methods/
Import/Export: http://ecb.jrc.it/import-export/

**Selected Publications**


**TECHNICAL EUR REPORTS**


More Information

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The mission of the JRC is to provide customer-driven scientific and technical support for the conception, development, implementation and monitoring of EU policies. As a service of the European Commission, the JRC functions as a reference centre of science and technology for the Union. Close to the policy making process, it serves the common interest of the Member States, while being independent of special interests, whether private or national.