Minutes
of the
ECVAM/*ecopa* Stakeholder Workshop
on the Formation of National Consensus Platforms for Alternatives to Animal Testing in the New EU Members States and Candidate Countries
5-6 June 2004
Prague, Czech Republic

Welcome & Opening of the Stakeholder Workshop:

Prof. Hartung (Head of ECVAM) and Prof. Rogiers (Chairperson of ecopa) welcomed the 50 participants from the ten new EU Member States (Poland, Czech Republic, Slovakia, Slovenia, Hungary, Lithuania, Latvia, Estonia, Cyprus and Malta) and the two candidate countries (Bulgaria and Romania) calling this stakeholder workshop a great opportunity to exchange first hand information, to get to know each other and to establish contacts that would result in close cooperation and the formation of National Consensus Platforms on Alternatives.

Introduction to ECVAM and status of 3Rs methods in the EU: (Prof. T. Hartung, Head of ECVAM)

Prof. Hartung gave a short overview regarding the number of animals used in toxicology and other safety evaluations. He explained that a total of approximately 10 million animals were used in the EU per year out of which only 0.4 per cent were actually used in the field of cosmetics. The industry share was about 12 per cent while 25 per cent of all animals were being used for testing of vaccines. ECVAM is primarily challenged with the 7th Amendment of the Cosmetics Directive and the upcoming REACH legislation which both require alternative methods. Prof. Hartung then provided background information on ECVAM and briefly summarized its tasks as being charged with validation, applied research to support validation, running a database and most importantly serving as a communication link for alternative methods.

In addition, Prof. Hartung explained that ECVAM had undergone some reorganization including the recent set-up of various task forces in order to face the challenge as good as possible. Key areas are systemic toxicity, local toxicity, sensitisation, carcinogenicity, reproductive toxicity, toxicokinetics, ecotoxicology as well as biologicals. Besides there were also some cross-cutting activities mainly with respect to the SIS databases, QSARs and strategic developments.

Prof. Hartung then gave some practical examples in the field of local toxicity to illustrate what was already at hand. He explained that the phototoxicity and skin-eye corrosion tests had made it to the OECD-level in 2002.These two methods had undergone the entire process of pre-validation, validation, formal ECVAM Scientific Advisory statement and finally regulatory acceptance. He emphasized that, though these two methods did not represent tremendously huge numbers of animals, they did represent a proof of principle. They had proven that it was indeed possible to achieve an international agreement on the validity of an alternative method fully replacing an animal experiment.

Concerning the issue of acute toxicity testing Prof. Hartung referred to an ongoing joint ECVAM-ICCVAM validation study of two *in vitro* basal cytotoxicity assays that would enable to predict the starting dose to the tiered testing strategy for acute testing and to the A-Cute-Tox project of the 6th Framework Program. Turning to the issue of chronic toxicity he stressed that this field was unfortunately not as advanced yet. A workshop on long-term toxicity testing had been held in 1999 and a pilot study using flow-cell and static-cell bioreactors was launched afterwards. He added that there was an ongoing prevalidation of a new perfusion system developed in FP4.

He further explained that the EU project Predictomics is under ecopa direction dealing with the question of short-term in vitro assays for long term toxicity. The project comprises 14 partners from eight countries with a total of six work packages ranging from liver cell model developments to the optimisation of tools and analyses to the identification of toxicity markers. He then summed up the major objectives of this project. The project was aimed at developing advanced cell culture systems which as best possible would represent the human liver and kidney in vivo. It was furthermore intended to identify specific early mechanistic markers of toxin-induced cell alterations by using integrated genomic, proteomic and cytomic analysis. In addition the project would strive to establish and prevalidate a screening platform (cell systems together with analysis tools) that was unambiguously predictive of toxin-induced chronic renal and hepatic disease.

For reproductive toxicity, the ReProTect-project had just started under ECVAM management. It is aimed at combining reproductive toxicology, protection of animals and detection of reproductive toxicants. The main idea behind it is to break down the reproductive cycle. The project will focus on the different elements that are being assessed in a two generation study. Attention is paid not only to the in vivo assays but also to the kind of in vitro batteries that could potentially be used. He stressed that it was realized that there were indeed many in vitro tests that nobody had ever thought of as potentially being useable to replace animal tests although they were widely used in reproductive medicine.

He then explained that an assessment of these results leads to four areas of concern, that is pre- and post-natal development, fertility, implantation and a cross-cutting area of some technologies. The idea is to elaborate these findings towards a pre-validation of test and test strategies and combine it with strategic discussions on how to develop a respective conceptual framework.

Concerning the project's structure he added that there is an advisory board in place, headed by ecopa. The day-to-day scientific management is handled by ECVAM while the University of Tübingen is in charge of the overall coordination. The budget is 9 million Euros. In addition, the consortium of 35 partners is nicely balanced with respect to affiliations to stakeholders (academia, industry, animal welfare and government) as well as the involvement of SMEs and big companies.

In addition, he briefly mentioned to two ongoing activities in the areas of carcinogenicity as well as (Quantitative) Structure-Activity Relationships. Finally speaking of the ECVAM business plan, Prof. Hartung explained that there was a ten year program to meet the expectations from legislation with a focus on bundling of all stakeholder activities, and combining strategic and technical developments. In addition, ECVAM would be available for support in such areas as coaching of the development of alternatives, not the development itself, (pre-) validation in international collaborative studies, support for regulatory acceptance

and international harmonization. From industry he expected support by providing in-vivo data and reference chemicals as well as funding for the development of new alternatives.

ecopa: initiatives and platform formation:
(Prof. V. Rogiers, Chairperson of ecopa)

Prof. Rogiers explained that ecopa, the European Consensus Platform on 3-R Alternatives, is an international not-for-profit and non-governmental organisation, based in Belgium and complying with Belgium law. She stressed that is the only quadripartite organisation at the EU level, which is promoting the 3Rs at the European level, adding that ecopa serves as an umbrella organisation for the National Consensus Platforms (NCPs) on alternative methods. Speaking of NCPs, Prof. Rogiers briefly explained that these national organisations need to be legal entities in compliance with national laws. National consensus platforms must furthermore comprise the four stakeholders, e.g. academia, industry, animal welfare and government.

During the 3rd World Congress on Alternatives and Animal Use in the Life Sciences, a workshop was held in Bologna to discuss the existence and necessity of national platforms. She continued that the idea was then introduced to stimulate the formation of quadripartite platforms (consensus platforms) at the national level and to bring these together in a quadripartite organization at the EU level, namely ecopa.

Furthermore, Prof. Rogiers explained that the aims of ecopa are to facilitate the exchange of scientific information, expertise and experience between national platforms, academia, animal welfare, industry government and EU. In addition, ecopa was striving to enhance further development and implementation of 3R-methods in the EU as well as worldwide and to raise public, governmental and scientific awareness for a better acceptance of alternative methods.

Regarding the tools to achieve these goals, Prof. Rogiers said that conferences, seminars, publications as well as scientific and educational initiatives are used. The collection and circulation of information, co-operative action, membership of relevant bodies and critical as well as scientific political statements are further means by which the goals of ecopa are pursued successfully.

At present, Prof. Rogiers explained that ecopa counts 14 Member State National Consensus Platforms; 11 full members being the platforms of Austria, Belgium, Czech Republic, Finland, Germany, Italy, The Netherlands, Spain, Sweden, Switzerland and United Kingdom and 3 associate members being Denmark, Norway and Poland. Furthermore, the first ecopa Board elections were held at the 4th ecopa workshop in November 2003. The board is composed of the President, Vice-President and Treasurer as well as 4 delegates and 3 3R-experts. In addition, she added that ecopa has 4 well established working groups. The main fields of interest are (I) the 6th Framework Programme of the EC for Research, Technological Development and Demonstration Activities, (II) the EC White Paper Strategy for a Future EU Chemicals Policy, (III) the formation & educational programmes on alternative methods within the EU, and (IV) the issue of ethics involving research with animals.

Then Prof. Rogiers turned to the question of why ecopa was needed in the past and would still be needed in the future. Speaking of the past, she pointed to the EU policies on chemicals, cosmetics and research as well as ECVAM's policy on alternative methods as good reasons. Speaking of why ecopa would also be needed in the future she referred to the EU policy on

chemicals and the environment (REACH & SCALE), the implementation of the cosmetics legislation as well as the drying up of sources for research into and resources for alternatives in general.

With respect to REACH she added that there was no agreement yet but it was obvious that alternative methods were not considered appropriately and realistically. Referring to SCALE she added that the near future would bring a new focus on environmental safety and children's health that could result in additional animal testing if sufficient alternatives were not developed.

Regarding the 7th Amendment to the EU Cosmetics Directive she explained that all animal testing would have to end by March 2009 with three exceptions for reproductive toxicity, biokinetics and repeated dose toxicity for which a ban would come into effect in March 2013. Prof. Rogiers stressed that this was not realistic, given the fact that the process of test development, validation and implementation into legislation is long and takes 6-8 years on average.

Referring to the 3R-alternatives that are actually available in the EU for regulatory testing she stressed that there are in effect only three corrosivity tests (TER, Epi Skin, Epiderm) and 1 phototoxicity test (3T3 NRU-PT). In addition there are 6 methods that are accepted by ESAC but not taken up in EU legislation yet being 1 skin sensitisation test (LLNA), 1 in vitro percutaneous absorption test, 1 additional corrosivity test (Corrositex), and 3 embryotoxicity tests (WEC, MM, ECT). Further tests under development and validation are in the fields of skin irritation,eye irritation, acute (oral) toxicityskin corrosion (in silico) and reproductive toxicity. Yet there are no alternatives for photo allergy, subacute toxicity, chronic toxicity, target organ and systemic toxicity, biokinetics and non-genotoxic carcinogenicity. Concerning funding of research projects on 3R-alternatives in FP6, Prof. Rogiers stated that the field covered is narrow and the number of projects limited. She concluded that more action is needed with respect to FP7. Yet, while action by individual pressure groups is useful, she felt that past experience has shown that bundled action by four stakeholders is much more effective and powerful. Closing her presentation, Prof. Rogiers expressed her hope that new NCPs would soon be established in the new EU Member States with the experience and help of ecopa.

Platform formation in new EU Member States

The Czech Story:
(Dr. Jírová, Chairperson of Czecopa)

Dr. Jírová explained that the idea to form a Czech national consensus platform was born in the wake of the 1999 World Congress on Alternatives in Bologna and the following first two ecopa workshops held in Brussels in 2000 and 2001. The subsequent discussions within the Czech Republic led to the formation of CZECOPA in November 2001. She stressed that CZECOPA is the only platform in the Czech Republic based on the four parties and adhering to the 3Rs principles.

She then illustrated that the activities between 2002 and early 2003 had focused on the registration and establishment of CZECOPA as a not-for profit organisation. During this period the statutes were produced, a general assembly was convened and representatives

elected. In addition a working plan with respective priorities was elaborated. She added that a website and logo were also under construction.

She described the short term objectives of CZECOPA as providing the public with information on its mission, setting up permanent communication between the 4 parties involved, implementing validated and valid alternative methods, and introducing alternatives in routine practice (testing labs/education). Furthermore, the long term objectives were to promote the scientific development and implementation of alternatives as well as to promote information and education. CZECOPA would also provide scientific support for responsible authorities and legislation

Regarding the support of legislative actions, Dr. Jírová said that CZECOPA had given support with respect to the update of the Animal Protection Act 246/1992 Coll., and demanded improvements regarding the implementation of alternatives and the registration of alternative methods. Furthermore, CZECOPA was heavily involved in the exact transposition of wording for the 7th Amendment of the Cosmetic Directive.

Concerning the promotion of education and information, she explained that CZECOPA was focused on broad public information at the initiative of animal welfare organizations. Leaflets and brochures on alternative methods were prepared, books translated and a number of public meetings held. Regarding alternatives at schools and universities, she reported that practical demonstrations of in vitro methods were introduced at the Medical Faculty of Charles University in Hradec Králové and EuroNICHE had become a part of regular education at the 3rd Medical Faculty of Charles University in Prague. Furthermore, demonstrations of photodynamic reactions in cell cultures took place at the Medical Faculty of Palacký University in Olomouc while a broader participation of students in veterinary practice instead of animal experiments was being promoted at the Veterinary and Pharmaceutical University in Brno.

Scientific development and implementation of methods are mainly present in the laboratories at the National Institute of Public Health in Prague where cytotoxicity and phototoxicity tests in vitro are performed and the 3D human skin models have been introduced: At the Department of Physiology (Czech Academy of Sciences Prague) photodynamic effects are performed in cell culture and alternative multimedia are used in students courses.

Members of CZECOPA died participate in workshops and symposia giving scientific presentations such as the conferences on Alternatives 2002 (Prague) and Alternatives 2003 (Poland). Finally, with respect to industry, Dr. Jírová added that results are presented to facilitate the introduction of alternatives to practice of testing laboratories such as the routine testing of medical devices, cosmetics, items of common use, chemicals (BIOTEST, ITC, NIPH). Presentations of alternative methods results are given at regular industry meetings and workshops of PROKOS and CSZV.

Dr. Jírová closed by saying that the focus in 2004 would be on strengthening the technical background (website, logo), promoting a broad introduction of alternatives, participating in research projects, giving scientific presentations and serving as a consultant for legislation.

Actual efforts by Poland
(Dr. M. Stepnik, representative Poland)

Dr. Stepnik explained that major efforts had been made over the past months to find stakeholders from all four groups (industry, academia, animal welfare and government) interested in forming a Polish NCP. He then provided more background information on the partners that had already agreed to take part.

Regarding industry, Dr. Stepnik said that the Dr. Irena Eris Cosmetic Laboratories with 247 employees and a turnover of 18 million Euros in 2003 and the Polish Confederation of Private Employers gathering 3000 private companies of different branches employing 500,000 people are present in the formation of a Polish NCP. He added that the Confederation is also a member of Polish Tripartite Commission for Socio-Economic Affairs composed of representatives of government, employees' and employers' parties thus being the most important national platform of social dialogue.

Turning to animal welfare organisations, Dr. Stepnik illustrated that the Polish Society for the Protection of Animals ("SPA") is actively involved in the formation of the NCP. He explained that the SPA cooperates with the World Society for the Protection of Animals (WSPA) and the Royal Society for the Prevention of Cruelty to Animals (RSPCA). Furthermore the SPA is a key actor in Lobbying for and passing of the Act on the Protection of Animals in 1997. The SPA has also participated in numerous ministry commissions working on the creation of the legal particulars – it provided more than 100 legal opinions and created several decree projects. The Society has more than 100 local offices in Poland.

Speaking of government institutions or organisations that are actively involved in establishing the NCP, Dr. Stepnik referred to the National Institute of Hygiene, the Bureau for Chemical Substances and Preparations and the Pszczyna Branch of Institute of Organic Industry.

He explained that the National Institute of Hygiene is directly responsible to the Polish Ministry of Health and conducts research and provides expertise service in the area of hygiene, microbiology, parasitology, food and environmental toxicology, epidemiology, and medical statistics. In addition, the institute issues opinions and certificates of newly introduced food products, dietetic products, food additives, contaminants, cosmetics, washing and cleaning agents, packages etc. It takes part in the preparation and evaluation of legislative acts and standardization documents on national as well as international level and participates in works of the Polish Committee of Standardization

The Bureau for Chemical Substances and Preparations is responsible for the control and assessment of chemicals; directed by the Inspector responsible to the Polish Minister of Health. It was created to harmonize Polish legislation regulating the marketing and use of chemicals with the analogous EU legislation. The key statutory duties comprise the collection of notifications of new substances, the provision of data concerning dangerous substances and preparations to medical and emergency services and the exchange of information on new substances with the European Commission and relevant authorities of the EU member states.

With respect to the Pszczyna Branch of Institute of Organic Industry Dr. Stepnik explained that the institute closely cooperates with national and foreign industry companies in the field of toxicological and ecotoxicological research. He added that the Departments of Toxicological Research and Ecotoxicology are compliant with GLP OECD and entitled to

conduct tests of industry chemicals, plant protection chemicals, cosmetics, drugs (including veterinary), food and fodder additives, industrial waste, and household chemicals. The Branch was appointed by the Ministry of Health for cooperation with Bureau for Chemical Substances and Preparations in the area of risk assessment after chemical exposure.

Turning to academia, Dr. Stepnik illustrated that the Department of Transplantology and The Central Tissue Bank of the Medical University Warsaw are involved with Dr. Śladowski being the key contact person. Dr Śladowski is a member of ERGATT, founder member and representative for central and eastern Europe of ESTIV (European Society of Toxicology in Vitro),and visiting scientist at the JRC. Furthermore, the National Centre for Alternative Methods in Toxicity Assessment is a second key player from academia. Dr. Stepnik said that in 1999 a programme supported by the Ministry of Health lead to the establishment of the "The National Centre for Alternative Methods in Toxicity Assessment" (NCAM) at the Nofer Institute of Occupational Medicine.

The aim of NCAM was the dissemination of the idea of applying alternative methods for toxicity assessment to replace, reduce and/or refine experiments on animals. Thus the main objectives were the collection and distribution of data on the concept and use of alternative methods, the promotion of the co-operation research centres employing the alternative methods and the Information exchange on research projects conducted in Poland and in other countries. Additional objectives were the organisation of workshops and conferences as well as the editing and distribution of the newsletter "Vitryna".

He further explained that the "Vitryna" quarterly is an official publication of the National Centre of Alternative Methods in Toxicity Assessment, being supported by the Ministry of Health under a long-term governmental programme called "Health and Safety in Work Environment". He added that the newsletter contains information on the history and development of the 3R concept, information on the implementation of alternative methods in research centres and their promotion among scientists in Poland, information of the activities of the National and Regional Ethics Committees. In addition, the newsletter contains international news on the activities of ECVAM and national centres for alternative methods as well as information on institutions employing alternative methods and legislation regarding alternatives to animal testing, etc. Dr. Stepnik added that there was also a home page available that among others provided reports on activities of Polish research centres employing alternative methods.

Closing his presentation Dr. Stepnik added that further potential partners from academia (Polish National Committee for the International Council for Laboratory Science) and government (The National Poison Information Centre, Central Registry of Cosmetics) are to be contacted yet. He added that legislative aspects are now in the centre of attention like drafting the statutes in accordance with the Act on Associations of 1989 and finally registering the NCP in the National Court Register.

Recent project realisations of ecopa
(Dr. B. Garthoff, Vice-Chairperson ecopa)

Dr. Garthoff commenced by stressing that ecopa is not part of the European Commission, hence neutral, but part of the political EU-scene and an NGO. Projects were being realized by taking action and by developing political impact! Regarding ecopa's finances and funding of activities he stressed that different sponsors had contributed over the past years ranging from

government institutions and ministries to national consensus platforms and private companies. In this respect, emphasis was put on having sponsors from the different parties concerned to avoid any financial dependence on one source that might result in attempts to exercise political pressure on ecopa. Yet, above all, he stressed that private initiative and enthusiasm were key factors in developing the association and achieving the goals.

Furthermore, Dr. Garthoff gave some examples of ecopa's key activities like the annual workshop, political statements, actions and projects. Regarding the annual workshop he explained that the general concept is to discuss issues of alternative method development, problems in in vivo-testing and 3-Rs (Refine, Replace, Reduce) aspects. It is the intention to address a different subject each year such as REACH, the White Paper on Chemical Policy, OECD guidelines, etc. The annual workshop is the place to develop actions on the basis of these discussions in order to take a political stand and to provide for a scientific exchange forum.

Another means of making ecopa's voice heard in the political arena is the development and dissemination of political statements to key political actors like the DGs (RTD, ENV, ENT). In this regard ecopa has produced a determined declaration combined with a successful internet sign-in campaign for increased funding of alternative methods development in 6th Framework Program (FP6) due to the implications for more testing requirements in the REACH programme. As a result, the EU Commission responded with a Stakeholder‘s Meeting in July 2002 and accepted projects under that heading in the 6th Framework Programme which had definitely not been foreseen before.

Regarding the participation in EU-projects, Dr. Garthoff explained that on the occasion of the preparations FP6, scientists were asked by the Commission to forward an "Expression of Interest (EoI)", showing potential 3-R-research proposals. ecopa submitted a total of 16 EoI collected in the different ecopa member countries. Dr. Garthoff added that ***ecopa*** had been quite successful in this regard since it was now in charge of coordinating the CONAM project (a specific support action – SSA). Furthermore, ***ecopa*** was selected to serve on the Management Boards of the 'ReProTect' (IP) and 'Predictomics' (STREP) projects as well as the Advisory Board of the 'A-Cute-Tox' (IP) project. In addition, scientists of ***ecopa*** member institutions would serve as research partners in the 'Predictomics', 'ReProTect' and 'A-Cute-Tox' projects.

Providing further information on CONAM, Dr. Garthoff explained that this project was about consensus networking on alternative methods within Europe. The main objectives are to build a solid network on 3R-alternatives and to exchange information (scientific, societal, and technological) on the development and validation of 3R-alternatives. He then illustrated the main topics to be covered as part of the CONAM-project as being the formation of new NCPs, in particular in the new EU member states and candidate countries, the creation of a newsletter on 3R-alternatives and the expansion of the ecopa website as well as the organisation of workshops and meetings. Further important topics would be to establish links with other FP6 projects on 3Rs, to report on the "-omics" field, and to stimulate international cooperation.

Dr. Garthoff added that a strong managerial and organisational back-up of the project was needed and had been regarded a vital component by the European Commission. To this end, he pointed out that ecopa was well prepared since there were already four working groups in place. One working group deals with consensus networking on 3R-alternatives, with Prof. Rogiers as the team leader, while the second one works on the EU White Paper on Chemicals

and is headed by Mrs. Karin Gabrielson. The third working group deals with education and training matters being headed by Dr. Jan van der Valk while the fourth working group is concerned with issues in the field of ethics with Prof. Tjard de Cock Buning being the team leader. In addition, the ecopa board is in charge of the day-to-day management tasks with three of its members (Prof. Rogiers, Prof. Castell, and himself) being responsible for the follow-up of the CONAM-project.

With respect to upcoming ecopa activities, Dr. Garthoff gave a brief summary of eSI, the „***e****copa***S**cience**I**nitiative", explaining that its aim is to reach top scientists of different research areas that might be relevant to alternative method development, and to organise a workshop with them. Further activities would be to invite young scientists and to initiate exchange by Science Fairs. The goal of eSI is thus to draw the best science to initiate „thinking about and for alternatives", to improve recognition of science in that area and to get the „alternative method research"out of the corner of mediocre science. Furthermore, to organize the funding and PR around it, and to hold science fora to foster exchange with other basic research scientists and scientists of NCPs and ECVAM. To this end, a workshop is planned in Spain near Alicante from 28th to 30th of October 2004. It is intended to have about 40 people attending of whom 4 would be major, well known senior scientists and 4 "applying" experts in their fields of expertise while the other 32 participants would be young scientists and researchers.

Dr. Garthoff then said that the next ecopa annual workshop will be held in Brussels from 26th to 28th of November 2004 and will focus on SCALE explaining that this new initiative is the EU's plan to provide adequate protection of children from exposure to harmful chemicals. He illustrated that a first unpublished draft for an action plan had been produced in spring 2004 putting major emphasis on the extended use of the precautionary principle. This among other factors could result in another major testing approach on top of REACH with significant testing in lab animals for safety, risk and hazard concerns. Therefore, it was decided by ecopa that the annual workshop would deal with this issue and that a statement and sign-in campaign on the website would be organized as had been the case with respect to REACH.

Closing his presentation, Dr. Garthoff stressed that ecopa realized projects by scientific and political action and that it had achieved impact as the EU representative umbrella organisation for alternatives by taking the initiative.

Recent project realisations of ECVAM
(M. Halder, scientific officer ECVAM)

Dr. Halder pointed out that the stages in the evolution of regulatory testing comprises research, development, prevalidation, validation, independent review, regulatory acceptance and implementation. She added that formal validation is necessary when the introduction of new tests would alter existing legislation like EU directives, OECD guidelines, European Pharmacopoeia monographs etc.

Dr. Halder then explained that an alternative (replacement) test can be regarded as the combination of a test system and a prediction model. She added that a prediction model (PM) is an explicit decision-making rule for converting the results of one or more alternative tests into a prediction of an in vivo endpoint. She also pointed out that there are major problems in validation studies. Quite often the goals of the study are not sufficiently defined or studies

poorly designed, planned and managed. Furthermore responsibilities of the participants are not clearly defined or SOPs are not available or not strictly followed.

Speaking of the criteria for test development, Dr. Halder stressed that the following information should be at hand for entry into (pre)validation. There should be information on the scientific purpose and proposed practical application, the scientific basis and case for its relevance. In addition, there should be an optimised protocol, including standard operation procedures, endpoints, endpoint measurement, derivation and expression of results, a prediction model and the inclusion of adequate controls. There should also be information on the limitations, domain of applicability and evidence of reproducibility.

Turning to prevalidation, she illustrated that a prevalidation study is a small-scale inter-laboratory study, carried out to ensure that the protocol of a test method is sufficiently optimised and standardised for inclusion in a formal validation study. The prevalidation process comprises three phases. In Phase I (Protocol Refinement), the protocol and the PM of a test method are refined in a single laboratory with previous experience in the use of the test. In Phase II (Protocol Transfer) an assessment is made of the ability to transfer the method to a second laboratory, making any necessary refinements to the protocol and prediction model. In Phase III (Protocol Performance) the relevance and the reliability of the test is assessed under blind conditions in three or more laboratories. At the end of Phase III a number of actions may be taken to progress to formal validation and to achieve readiness for incorporation into regulatory guidelines. Yet, it may also be necessary to develop further methods or to quit at this stage if the prevalidation has reached a dead end.

Speaking of validation, Dr. Halder explained that a validation study is a large-scale inter-laboratory study, designed to assess the reliability and relevance of an optimised method for a particular purpose. Reliability, relevance and the purpose are key factors at this stage. Reliability means the reproducibility of results within and between laboratories and over time. Relevance focuses on the scientific value and practical usefulness while the purpose concerns the intended application of the procedure. Dr. Halder continued that further important criteria for the validation process are the study design, the selection of tests and laboratories, the selection and distribution of samples and test reagents, the data collection and analysis, and the assessment of performance of test(s).

Dr. Halder stressed that the post-validation phase is marked by an independent assessment, and then regulatory acceptance. The publication of the study in a peer-reviewed journal, an assessment of the outcome by an independent expert panel and a statement on the validity by ESAC are key components. Regulatory acceptance means that a test guideline needed to be drafted and submitted to regulatory bodies to be followed by consultation with expert groups and eventual adoption and publication of the new test guideline.

Speaking of achievements, Dr. Halder illustrated that there are now accepted in vitro methods for skin corrosion, phototoxicity, percutaneous absorption, QC of tetanus and erysipelas vaccines as well as validated in vitro methods for pyrogenicity, embryotoxicity, haematotoxicity.

Dr. Halder then provided more information on the JRC Enlargement Action explaining that ECVAM's activities aims at starting and extending collaboration, providing training and providing and exchanging information by means of conferences, workshops, training visits and courses as well as technology transfer and research. She added that three conferences were held in Prague (2001); Warsaw and Budapest (2002) that provided general information

on ethical and legal background of the Three Rs and Directive 86/609/EEC as well as specific information on validation, alternative methods for the testing of chemicals, cosmetics, medical devices, biologicals etc. Regarding workshops, she added that one was held on the validation of alternative methods at ECVAM in 2001. Two workshops focused on alternatives to the use of animals in higher education (Piran /Slovenia in 2002 and Warsaw 2003) while a third one highlighted the use of QSAR in regulatory testing strategies (Prague 2002).

Dr. Halder pointed out that a number of practical training courses were organised that focused on in vitro methods for pyrogenicity testing (Budapest 2003) and in vitro production of monoclonal antibodies (NVI/The Netherlands 2004). Concerning technology transfer and research, she added that there is a project on the use of stem cells and reference models for developmental and chronic neurotoxicity testing in vitro involving the National Veterinary Research Institute & Medical Research Centre in Poland. The scientists involved participated in ECVAM's activities such as the conference in Warsaw or the training visit at ECVAM. The objective of this project is to optimise promising models for prevalidation.

Closing her presentation Dr. Halder referred to the activities of 2004 telling the participants that there will be training courses on Three R methods for the production and quality control of biologicals focusing on veterinary vaccines and in vitro production of monoclonal antibodies. Furthermore there will be a call for Visiting Scientists and Detached National Experts in the fields of QSARs, reproductive toxicology and ecotoxicology. There shall also be a call for PhD students and Post Docs to be published on the IHCP (Institute for Health and Consumer Protection) website.

EU funding with respect to alternative methods:
(Dr. B. Lucaroni, scientific officer DG RTD)

Dr. Lucaroni gave a short overview regarding the set-up of FP6 and outlining the areas in which the development of alternative methods was welcome. She explained that this was primarily the case with respect to the "Priority 1 area" (Life Sciences, Genomics and Biotechnology for health) as well as the anticipating needs as part of "Integrating European Research". In addition, alternatives development had its place in structuring ERA when dealing with Science and Society.

Referring to the Council Decision on 30/09/2002 regarding the specific programmes for FP6, she furthermore explained that a number of fields would not be funded such as research activity related to human cloning for reproductive purposes, research intended to modify the genetic heritage of human beings, studies to create human embryos solely for the purpose of research or for the purpose of stem cell procurement, including somatic cell nuclear transfer. But she also stressed that the use of banked or isolated human embryonic stem cells in culture was already being funded from the start of FP6.

Dr. Lucaroni explained that in Priority 1 (first and second call) in the area of new in vitro tests to replace animal experimentation, there were possibilities to apply for Integrated Projects (IP), a Specific Targeted Research Projects (STREP) and Specific Support Actions (SSA).

Dr. Lucaroni then referred to the first and second calls in the Priority 8 area, e.g. policy support and anticipating S&T needs. She informed the participants that in the context of the Commission's White Paper on a strategy for a future Chemicals' Policy, the Commission was committed to the promotion of non-animal test methods, through maximising use of non-

animal test methods, encouraging development of new non-animal test methods and minimising test programmes. To serve this purpose, both calls request proposals to carry out research on the development of alternative methods for testing chemicals, both at the European Community level and at the level of Member States, and to enhance and share the relevant information that could be obtained from testing.

After briefly explaining the different types of contracts (Integrated Projects, Specific Targeted Research Projects and Specific Support Actions), Dr. Lucaroni also stressed that there were some mandatory requirements that had to be fulfilled in the field of alternative tests development. The results generated should lead to the production of globally accepted test guidelines, statistically valid for formal validation purposes and dissemination of knowledge and competencies that could pave the way for their regulatory acceptance.

Dr. Lucaroni then gave a short overview with respect to the projects that are currently supported by the EU. Concerning the development of new in vitro tests to replace animal experimentation, she referred to the ReProTec-, Predictomics-, CONAM-, A-Cute-Tox-, NHRDevTox- and BBMO-projects. The ReProTect-project receives 9.1 million € and is focused on the combination and application of in vitro cell and sensor technologies in the field of animal in vivo toxicology. The Predictomics-project with a funding of 2,2 million € would strive for alternative in vitro tests promoting industrial competitiveness in the product screening and development process stages of pharmaceutically-relevant lead compounds. The CONAM-project would be funded with 150.000 € and serves as a forum on the achievements in raising awareness on the use of alternative methods in the new EU Member States and Candidate Countries. The A-Cute-Tox-project with a funding of 9 million € is aiming at an optimisation of test batteries for human acute toxicity. Finally the NHR Dev Tox- (144.000 €) and BBMO- projects (443.000 €) deals with the issue of non-animal test methods for chemicals, medicines, biologicals and biomaterial by means of a prospective analysis.

Turning to the Action Plan Science and Society, Dr. Lucaroni pointed out that alternatives research has its place specifically in Action 34 that focuses on the protection of animals used in scientific research. Though not directly linked to the development and validation of alternatives, there is a minor budget allotted to fund a study related to the ethical review and the implementation of the Three Rs in animal welfare.

Dr. Lucaroni turned to the “Priority 1 area” once more, explaining that there would be a third call for in vitro alternatives. This call would focus on proposals for cell systems to enhance toxicity testing (IP), optimization and pre-validation of in-vitro models for drug absorption, modification and detoxification (STREP), assessing the risk of chemical compound (SSA), mini-pigs as models for toxicity testing (SSA), and a socio-economic impact study of FP5 in-vitro contracts (SSA).

Finally, she provided several internet links as further information sources:
http://www.cordis.lu/fp6.html
http://www.cordis.lu/fp6/lifescihealth.htm
http://www.cordis.lu/fp6/instruments.htm
http://www.cordis.lu/fp6/subprop.htm
http//:www.cordis.lu/fp6/inco.htm

Discussion group/country

Prof. Castell gave a brief overview on points and aspects that need to be considered when working towards the formation of a national consensus platform. He gave some background information on statutory and legal aspects for becoming an associate or full member of ecopa and he also provided some information on experience gained from already existing platforms. He also stressed that new groups willing to form a platform would be assisted by ecopa. The participants then divided into three working groups to discuss the situation and potential changes as well as obstacles for founding national consensus platforms in their countries. The results were presented the during following day.

Day 2
Countries present the outcome of discussion

Czech Republic/Poland

Due to the well advanced status of both countries in establishing NCPs, the Czech Republic and Poland had formed together a separate working group comprising only the representatives of both countries. Dr. Stepnik presented the results on behalf of both platforms. He pointed out that the further extension of the respective platform websites posed a challenge mainly due to a lack of sufficient funding. It was contemplated that financial support should be secured by asking companies. Then another question to be solved in the near future was the issue how to design the national websites, either in a standardized way following the ecopa example or in a unique one that would conform to the platforms' needs.

Dr. Stepnik raised also the issue of membership fees for a NCP of the new EU countries explaining 100 € is too high. He further added that some elaboration was also needed with respect to accepting new members, e.g. written application, personal recommendation and/or admission by election/voting.

Furthermore, Dr. Stepnik stressed that different stakeholders had to be informed about the potential benefits of joining a national consensus platform suggesting that perhaps a logo to put on goods advertising alternative methods might appeal to industry. He also added that communication with the consumer must be increased to inform and convince them of alternative methods. He suggested the elaboration of a pro-consumer policy as a potential new task for ecopa. Finally, Dr. Stepnik stressed that the members of both platforms would like to have more training activities.

Estonia

Dr. Lang explained the situation in Estonia and said that industry does not significantly use animals. This is the case pharmaceutical industry and the cosmetics industry. Regarding the chemical industry he added that traditionally testing is performed in other countries. Since restructuring has taken most of the free resources, he doubted that there would be much interest by industry to contribute to a platform. Yet, he felt that if alternative methods were easy and inexpensive to use the studies could also be performed within the country.

Concerning government, he stressed that it had other priorities at the moment. He added that the Animal Protection Act is giving regulation about the use of experimental animals. In application forms for studies, involving animal experiments, there is a question about the possibility to use alternatives instead of laboratory animals. Besides, he thought that some future needs for developing alternatives would be driven by the new cosmetics legislation. Turning to academia, Dr. Lang said that there is the biggest potential and interest. Some scientific groups are involved in 3R-related projects and alternative methods are being used, but on a limited basis due to a lack of funding and experience. Referring to animal welfare groups, he explained that there is no “drastic” animal protection activity in Estonia.

With respect to the formation of a national consensus platform in Estonia, he saw a major problem in the small size and population of the country. Due to this fact it was difficult for the concerned stakeholders to cover all possible areas and in effect there were too few people actively involved in laboratory animal science. Given this background he felt that Toxicologists and Laboratory Animal Science Society related people were the most likely to take the lead in forming a platform in Estonia. Yet, it would not be easy to get the other stakeholders.

Hungary

Ms. Molnar stated that all four stakeholders present at this workshop were interested in forming a national consensus platform in Hungary. The current needs for the formation of a platform were to find a team leader, to look for funding, to gain more knowledge on ecopa as well as support from leading scientists and experts. Furthermore, it would be necessary to contact the relevant bodies and persons in government, academia, industry and animal welfare.

To this extent it would be very useful to have an official letter of confirmation from ecopa to stimulate more attention and interest when contacting the various stakeholders. Ms. Molnar also expressed interest to have an ecopa training course or workshop on alternatives organised in Hungary which could serve as a forum to bring all stakeholders together.

Bulgaria

Dr. Tsolova explained that Bulgaria has already transposed all relevant EU directives related to animal testing and that alternative methods have been implemented in toxicology testing. Regarding the economical situation of industry, she informed the participants that there had been a significant decline during the transition period. Pharmaceutical and cosmetics industry, however, did not suffer as much as the rest of the industry. Thus these could perhaps be interested in participating.

Dr. Tsolova said that currently there is insufficient knowledge on in vitro toxicology in industry and academia. Further problems were a lack of trained in vitro toxicologists, an insufficient awareness of government on alternatives as well as insufficient funding. It would therefore be necessary to establish a policy promoting the 3Rs and its implementation in toxicology testing and higher education as well as to collaborate in the development and validation of alternatives at a later stage.

Regarding the formation of a platform, she felt that a number of groups would be interested in joining the effort, like the Bulgarian Chamber of Chemical Industries, the Association of Cosmetics Industries, the Bulgarian Academy of Sciences, the Bulgarian Society of Toxicology, and the Bulgarian Ministries of Health, Agriculture and Economy and the animal welfare groups working on laboratory animals.

Dr. Tsolova stated that ecopa and ECVAM could help with training on specific alternative methods and the consultation of national experts on the national ethics committees.

Malta

Dr. Fenech explained that Malta is in a very particular situation due to the country's size. The population of Malta is 350.000 and there is only one university with 2-3 researchers doing animal experiments. Furthermore there is no animal related industry such as pharmaceutics or cosmetics. Animal welfare groups do exist but specialise in animals used for sports and breeding.

Yet, he was convinced that the creation of a national consensus platform was relevant for Malta since awareness for alternatives was needed for EU projects in FP6 etc. He explained that the MCST (Malta Council of Science and Technology) as the main council on science was probably the best suited forum to start discussions on setting up a platform. As a starting point, it would now be necessary to get in contact with academia to take the lead and then to get government and industry and animal welfare interested.

Cyprus

Prof. Constantinou informed the participants that Cyprus has one university that was founded 12 years ago. Furthermore, there is a semi-governmental research institute and a government run national chemicals laboratory. In addition, there are 1-2 cosmetics companies and 2 animal welfare groups.

He expressed his conviction that a platform could be formed with the help of ecopa, though he also felt that it would be difficult to get representatives from all stakeholders involved. Yet, he was very positive about the potential interest of government and academia despite the small size of the scientific community.

Prof. Constantinou announced that he would contact all potential partners, look for funding and introduce the idea of a platform at different conferences. In this respect, he pointed out that there will be a medical conference in September 2004 at which a session could be organised on topics like ecopa, the EU cosmetics legislation etc. Closing his presentation, Prof. Constantinou added that he would also appreciate to have an official letter of confirmation that he could show when contacting potential stakeholders.

Romania

Dr. Tofan explained that the relevant EU directives concerning the use of animals in experimentation and the use of alternatives have already been transposed into national laws. The application of the 3Rs, however, proves to be difficult due to the bad situation in

laboratories and the low funding. Nevertheless, a new discipline was introduced in 2002 that brought animal welfare and the protection of animals into the curriculum of institutions for higher education.

Furthermore, Dr. Tofan said that it would not be easy to form a platform due to the 4 party requirement. Yet, she felt that after the upcoming elections in Romania there would be increased interest with the Ministries of Agriculture and Health as well as the pharmaceutical and cosmetics industries. At present academia was the most interested party in forming a platform. She would therefore take the lead in contacting the relevant people at the various universities and other stakeholders as well. Closing her talk, she suggested that ecopa could organise a training course or workshop in Romania to stimulate the development there.

Slovenia

Dr. Cestnik said that the pharmaceutical and cosmetics industries would likely be less interested in forming a platform but that government (Ministries of Education & Science, Public Health, Agriculture and Environment) is interested. Academia with four universities and 5 relevant institutes would probably form the nucleus for establishing this platform. The animal welfare groups, however interested, may have problems to accept the working basis that all three Rs have the same relevance. Another problem might be that due to the country's small size, there are not too many people to get involved in order to shoulder the burden of additional work. Nevertheless, Dr. Cestnik expressed his hope that a platform could be founded within the next 3 to 4 years. Finally, he stated that ecopa could assist by sending people to workshops and conferences in Slovenia to give lectures on 3R-related topics, ecopa etc.

Lithuania

Dr. Noreikis stated that there is only one animal welfare group in the country but this one is definitely interested in establishing a platform. Concerning industry he figured that the cosmetics and household products association was the most likely to support ecopa. With respect to government he said that the Ministry of Health, Environment and Agriculture could possibly be interested. Turning to academia, he added that Vilnius University, the Lithuanian Veterinary Association and others could be interested and would indeed most likely be the ones to take the lead.

He thought that a platform could be formed within the next 2 to 3 years but that there were also quite some issues to be resolved beforehand. One possible problem could be to raise awareness for the issue since animal use has dropped over the past ten years by 80 per cent. Another issue might be to get all four stakeholders involved and to get funding which would have to come from government and industry since academia and animal welfare do not have such means.

Closing his talk, Dr. Noreikis said that ecopa could help by providing further information on the statutes, by organising training courses, by sending a representative to lobby for support of the platform and to waive the membership fee in the beginning of ecopa membership.

Latvia

Dr. Kocina explained that Latvia has already transposed all relevant EU directives in this field and passed laws on keeping and using animals in 2002 and on the establishment of an ethics council in 2003. She furthermore informed the participants that animal use had dropped significantly over the past years since industry does not use any animals, and academia is badly under-funded to run many studies that would involve the use of animals. There are currently two animal houses with laboratory animals in Latvia but they may have to be closed in the future. For this reason there is also no public debate on the use of laboratory animals and animal welfare groups are preoccupied with cats, dogs and farm animals.

It will therefore be very difficult, though not impossible, to form a platform. Dr. Kocina thought that the ethical council was the best suited in Latvia to take the lead and that a platform could possibly established within 3 to 5 years time.

Slovakia

Prof. Augustin said that he was prepared to start with organising a platform and that one of the research institutes of human or veterinary medicine in Bratislava was most likely to serve as a nucleus. He noted that the Czech experience would be of great help in this respect.

Prof Augustin then explained he would contact the relevant stakeholders to get their support for this initiative. With respect to government, he said that the Ministries of Health and Education needed to be contacted but also pressured to participate. Concerning academia he felt that there is already a strong interest and willingness to go ahead (State Institute for Pharmaceutics Testing, Institute of Preventive Medicine, Slovak Academy of Sciences and universities). As far as industry goes, he thought that Slovak Pharma, Degussa as well as the petroleum and chemical industries could be interested, though this would not be an easy task. With respect to animal welfare groups it would still be necessary to find the relevant contact persons.

Ending his talk he added that the organisation of educational programmes on alternatives should be one priority to work on in which the help of ecopa and ECVAM would be most welcome.

Final conclusions and further steps to be taken

Summing up the presentations given by the different speakers, Prof. Rogiers stated that the participants interested in forming a platform should contact her and prepare a list in which they define their particular needs including training courses and workshops so that ecopa can assist on an individual basis. Furthermore, a letter of confirmation – as suggested by various speakers – would be prepared and made available by ecopa. It was also agreed that no membership fee would be asked, at least not in the first two years of existence of a platform from the new EU Member States. It was also promised that ecopa would look for industrial partners that could help the start-up of NCPs.

Closing the workshop Prof. Rogiers and Prof. Hartung thanked the participants and expressed their hope that this event was just the beginning of a long lasting and successful cooperation that would eventually lead to the creation of new ecopa National Consensus Platforms throughout the new EU Member States.