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JOINT RESEARCH CENTRE

Institute for Health and Consumer Protection
European Centre for the Validation of Alternative Methods (ECVAM)

ECVAM Stakeholder Forum

ESTAF

1st Meeting of the ESTAF

27 May 2011

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Draft Minutes

Minutes: Claudius Griesinger (ESAC/ESTAF Coordination)

Contents

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Participants

Present:

1. ESTAF Representatives: Remi Bars (ECETOC), Roland Buesen (DGPT for Eurotox), Bart de Wever (IVTIP), Alison Gray (ESTIV), Robert Landsiedel (CEFIC, replacing Bruon Hubesch), Reinhard Kreiling (EFfCI), Kirsty Reid (Eurogroup for Animals), Hermann Schweinfurth (EFPIA), Laurie Scott (AISE), Troy Seidle (ECOPA and replacing, at this meeting, Emily McIvor for Humane Society International), Rob Taalman (COLIPA), Katy Taylor (ECEAE), Bjorg Pauling (EUPRIM-Net, replacing Stefan Treue)

2. Commission staff: JRC: Joachim Kreysa (HoU IVM), Maurice Whelan (HoU ST; participating in part), Sharon Munn (ECVAM Policy Support Coordinator), Claudius Griesinger (ESAC/ESTAF Coordination), Valerie Zuang (Competence Group Leader), Sandra Coecke (Competence Group Leader), Marlies Halder, Raffaella Corvi, Susanne Belz, Joao Barroso, Elise Grignard ENV: Susanna Louhimies

Marlies Halder, Juan Riego Sintes, Valérie Zuang, Sandra Coecke, Maria Pilar Prieto Pereita, Silvia Casati, George Kirmizidis, Raffaella Corvi, Alexandre Angers, Joao Barroso, Pascal Phrakonkham, Anita Tuomainen

Excused:

1. ESTAF Representatives: Helder Constantino (ADI), Emily McIvor (Humane Society).

2. Commission staff: JRC: Elke Anklam (Director IHCP), Juan Riego Sintes (EU National Coordinator for Test Methods); SANCO: Karin Kilian, RTD: Arnd Hoeveler, Jürgen Büsing, ENTR: Michel Bouvier-d'Yvoire,

Opening

The meeting was opened by the Chair (J. Kreysa, IVMU/ECVAM) who welcomed all participants, followed by a tour de table during which ESTAF representatives and Commission staff introduced themselves, presenting their personal background and affiliation.

In the absence of comments, the agenda (see Annex 1) was adopted.

1 Session 1: ESTAF – ECVAM's participatory approach to stakeholder involvement

1.1 Presentation ECVAM: ECVAM's mission, processes, advisory structure. Reasons and role for ESTAF

The presentation was entitled ***ECVAM's mission, processes and advisory structure, with particular emphasis on the reasons and role for ESTAF and PARERE*** and addressed the following 10 aspects, some of which are outlined in more detail below as they are particularly relevant for ESTAF's self-concept and operation:

1. ***The historical background to ECVAM*** (original Directive 86/609, Commission communication setting-up ECVAM (SEC 92 1794)
2. ***ECVAM's mission and internal structure***
3. ***Key present legislative drivers of ECVAM's work*** (REACH, Cosmetics Directive, Experimental Animal Directive 2010/63)
4. ***Recent developments with regard to ECVAM's status***: ECVAM is now the EU reference laboratory for the validation of alternative methods (Dir 2010/63).
5. ***ECVAM's advisory structure***: PARERE, ICATM (=International Cooperation on Alternative Test Methods), ESTAF, ESAC (=ECVAM Scientific Advisory Committee)
6. ***ECVAM's stakeholder analysis:*** key stakeholder groups within its stakeholder community.
7. ***Legislative anchor for PARERE and ESTAF*** in Directive 2010/63/EU (Whereas 47, Article 47, Annex VII) and roles of PARERE and ESTAF.
8. ***ECVAM validation process and how the input from PARERE and ESTAF is used within this process*** (priority setting of test methods entering validation)
9. ***ESTAF's and PARERE's roles***: overlap and differences.
10. ***The practical aspects of ESTAF's input on user relevance of proposed test methods***

Points 1, 2 and 4 are described in more detail in Annex 2. Information on the ECVAM advisory structure including the roles and responsibilities of PARERE and ESTAF are reproduced below as communicated during the meeting.

Advisory Structure of ECVAM

It was explained that the previously existing **ECVAM Scientific Advisory Committee** (**ESAC**), which used to be comprised of representatives of the Member States, relevant industrial associations, academic toxicologists, animal welfare organisations and other Commission services, had been reformed and

restructured in order to separate the provision of independent scientific advice from any vested interests. Consequently, the ESAC had been renewed in 2010 now consisting solely of senior scientists selected on the basis of their scientific expertise who are required to act independently, free from any third party influence, and only on the basis of scientific considerations. Dialogue with the Stakeholder community is maintained by the **ECVAM Stakeholder Forum (ESTAF).** In parallel, the **PARERE** network had been established to advise ECVAM on the regulatory relevance of alternative test methods submitted to ECVAM for validation. This network is in fact composed of two networks: (1) the network of member state contact points (as stipulated in the new Directive 2010/63) and (2) an Interservice network consisting of relevant Directorate Generals of the Commission (DG JRC, ENV, ENTR, SANCO, RTD) and relevant EU agencies that have a stake in alternative methods (EMA, EFSA, ECHA).

Roles and tasks of PARERE & ESTAF

While the roles of the PARERE network and the ESTAF overlap with regard to input on test methods, the general objective of the ESTAF is centred on the issue of maintaining close bi-directional dialogue with the stakeholder community.

ESTAF's roles were summarised as follows:

1. Advocacy, voicing of stakeholder interests (e.g. economical, societal, specific etc.)
2. Maintaining close dialogue with and between stakeholders concerning inter alia new activities, trends, scientific and technical issues, forward-looking aspects of test method development, optimisation, validation and use.
3. Serving as a collaborative platform in view of supporting ESTAF's and ECVAM's activities
4. Input on test method relevance (stakeholders view) and draft ECVAM recommendations. The input on overall test method relevance will be used for priority-setting of validation studies coordinated or evaluated by ECVAM.

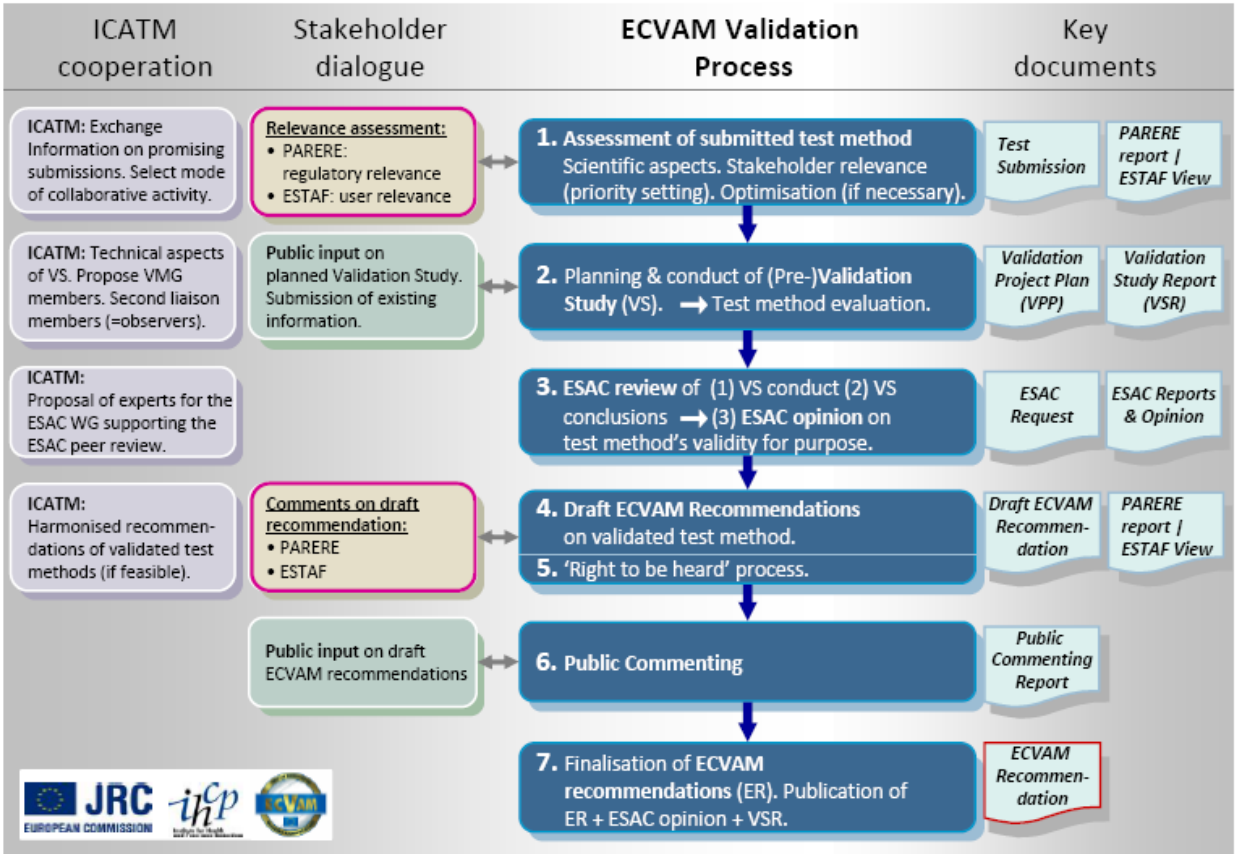
PARERE's roles were summarised as follows:

1. Upstream input on potential regulatory relevance and suitability of proposed test methods across different regulatory frameworks. This should include the facilitation of timely information flow from /to regulators in in relation to alternative methods under development and taking account of the respective regulatory needs during validation. Furthermore, early involvement of regulators should support awareness and buy-in for alternative methods in the pipeline.
2. Identification of regulatory experts that could participate in specific ECVAM project groups and provide specific regulatory expertise (e.g. chemical selection, applicability, limitations etc.)
3. Commenting on draft ECVAM recommendations following ESAC Peer Review of Validation Studies.
4. Dialogue – if necessary – during validation (technical/scientific issues)

ECVAM Validation Process

The ECVAM validation process was presented to ESTAF as a seven step process (see graphic below) in which ESTAF and PARERE was explicitly involved in steps 1 and 4, step 1 being the assessment of a submitted test method and step 4 the draft ECVAM recommendation based on the outcome of the validation study. In addition ESTAF representatives could also be asked for input along the validation process (e.g. suggesting suitable experts in a specific area for which the test method, selection of test chemicals in view applicability of a method etc.).

FIGURE 1 *Schematic depiction of the ECVAM validation process, the key documents and key interactions with the stakeholder community (General public, ESTAF, PARERE) and within the context of the ICATM cooperative framework (ICATM=International Cooperation on Alternative Methods; a cooperative framework involving validation bodies from EU, US, Japan, Canada and Korea).*



Practical organisation of input during step 1 and 4 of the process

The process flow for the first consultation step was indicated in more detail as illustrated below (Figure 2). It begins when a test submitter indicates an interest to submit a test method for validation by providing information on the test method, the underlying test system, the parameters measured, the intended purpose, the possible impact on 3Rs and level of optimisation/development, following a test pre-submission format (TPF) provided by ECVAM. On the basis of this information, ECVAM performs a preliminary assessment and if the outcome is positive requests the test submitter to make a submission of all other relevant data demonstrating performance of the method and ***at the same time*** shares the information provided in the TPF and ECVAM's preliminary conclusions with the **PARERE and ESTAF**. The information is also shared with other validation organisations (ICATM) to solicit their interest to be involved in any subsequent validation activity, and establish if they had also received any similar submissions.

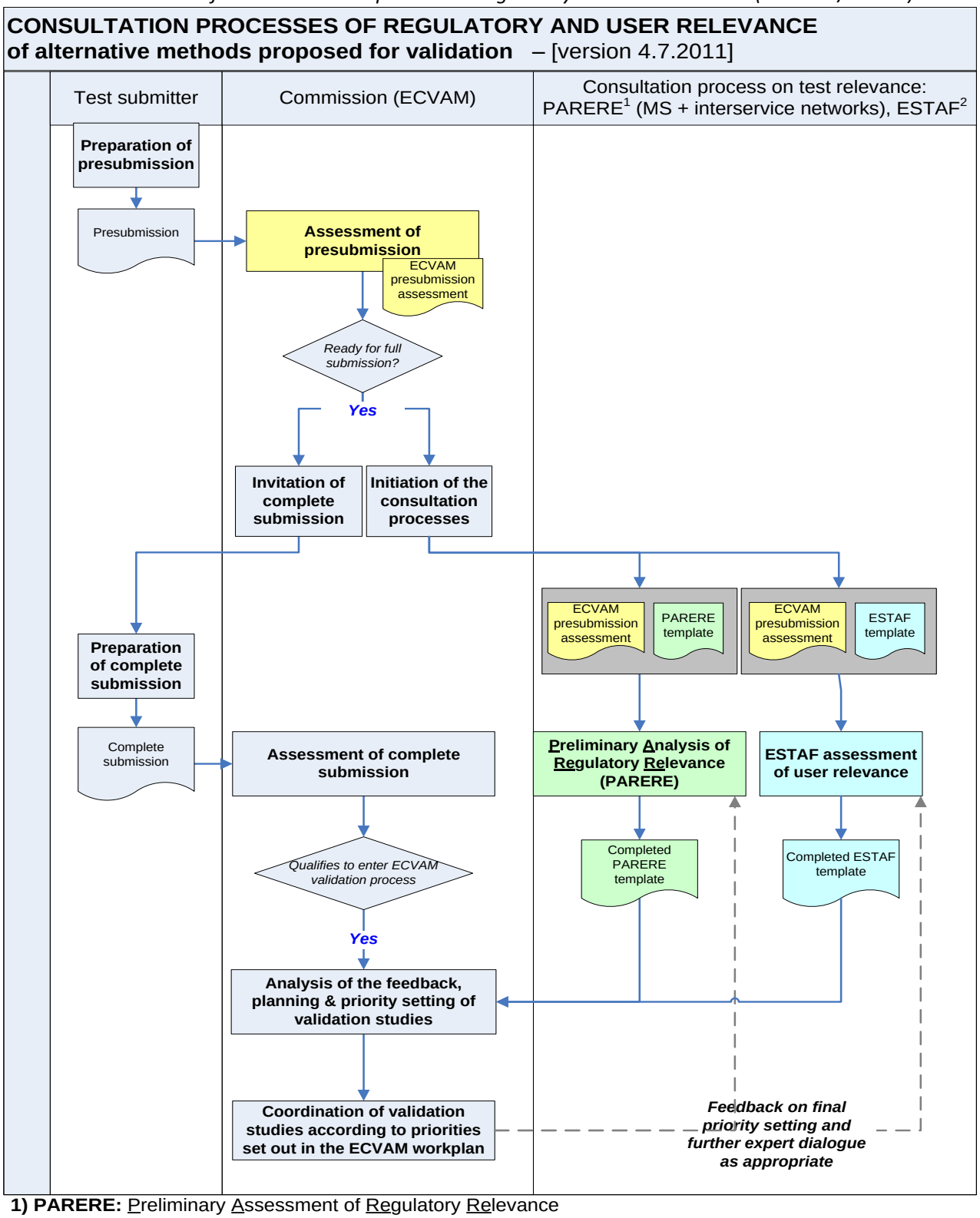
Each member of the PARERE network should act as a coordinator of their own internal national networks to gather the views from each of the competent authorities responsible for the different regulatory areas requiring safety assessment. Similarly, ESTAF representatives may either provide their own view to ECVAM, or involve others from their respective stakeholder organisations. PARERE's views on regulatory relevance should be captured via a score from 1 to 10 on degree of relevance for each regulatory domain including a justification of the score. The views would only be seen as preliminary and not binding as they would be made on the basis of very limited information.

ESTAF would be asked to provide a preliminary view on relevance of the method from a user's point of view by compiling a response template (a draft of this template had been circulated before the meeting and as a room document during the ESTAF meeting) that addresses aspects of

- Regulatory relevance and relevance for applied research, basic research and education and training
- Particular strengths / weaknesses of the proposed method (scientific aspects but also practical issues relating to conducting the test on a routine basis)
- Ethical considerations (mainly 3Rs)
- Economical considerations
- Suggested additional applications of the proposed test method (also within other regulatory contexts that the test submitter or ECVAM may not have been aware of)

The responses from PARERE and ESTAF would be fed into ECVAM's priority setting process for planning the work programme, which would include other considerations such as availability of laboratories to conduct the validation studies.

FIGURE 2: *Flow chart of the consultation process on regulatory and user relevance (PARERE / ESTAF)*



1) PARERE: Preliminary Assessment of Regulatory Relevance
2) ESTAF: ECVAM Stakeholder Forum

1.2 Discussion

- In response to a question on how PARERE was set-up and how it was composed, it was explained that in order to expedite the process of regulatory acceptance of alternative methods, it had been considered that regulators should be involved as early as possible in providing a preliminary view on the potential regulatory relevance of methods submitted to ECVAM for validation. This was reflected by the new elements introduced into the recently revised EU directive on the protection of animals used for scientific purposes (2010/63/EU) highlighting the reference in Chapter V, Article 47 (5) on alternative approaches stating that *''Member States shall nominate a single point of contact to provide advice on the regulatory relevance and suitability of alternative approaches proposed for validation''*.
    - In October 2010, Member States had been invited by the Commission to nominate such single points of contact and these nominated representatives formed the network of Member States.
    - In addition, since it was also considered important to involve the EU regulatory agencies, requests for nominations from EFSA, ECHA, EMA and the DG SANCO Scientific Committees had also been made. This part of the PARERE network being referred to as *''Interservice Network''.*
    - These representatives from both Member States and EC regulatory bodies/agencies, had convened the day before the ESTAF meeting for their first meeting. Together the two networks constituted the Preliminary Assessment of Regulatory Relevance network, otherwise known as PARERE.

  The Member State requirements according to Art.47 of directive 2010/63 were furthermore explained. These require Member States ***to contribute*** to the development and validation of alternative approaches and to identify laboratories that are suitably specialised and qualified to carry out validation studies. The COM was tasked to set priorities and allocate tasks between these laboratories.

- With regard to the communication role of ECVAM, stakeholders suggested that ESTAF representatives should also be able to trigger discussion / communication on issues related to alternative methods and that the communication process should go both ways. ECVAM confirmed that the role of ESTAF was indeed also to provide input on issues perceived as critical by the stakeholder community. These could be discussed during ESTAF meetings or through written procedures.
- Stakeholders alerted to the necessity of reviewing the current validation paradigm and suggested that ESTAF be involved in possible discussions / activities of ECVAM. ECVAM confirmed that the intention was indeed to involve ESTAF in such aspects.
- Stakeholders requested whether they could – for reasons of networking with regulatory colleagues – have the list of the PARERE contact points. It was explained that prior to the distribution of the contact details, the Commission was obliged to clarify with the experts (Privacy of personal data). In any case, information on the MS ministries involved in the PARERE network could be distributed.
- Stakeholders asked whether the new element of PARERE meant that ECVAM would focus only on regulatory aspects. ECVAM stressed that while regulatory application of alternative test methods was of key importance due to the legislative drivers, ECVAM had, according to the revised Directive, also the duty to look into applications in the area of basic research and, possibly, education and training and the general principle of contributing to the 3Rs remains.

1.3 Summary presentations of the Stakeholder Organisations

Short summaries of the introductory presentations of the ESTAF member organisations are given in Annex 3. Summaries of the expectations / contributions of the Stakeholder organisations are reproduced below.

All ESTAF member organisations clearly demonstrated their interest in and most also outlined their expectations and potential contribution to the work of ECVAM (see below). The interest to constructively cooperate with each other and with ECVAM was very clear and visible and it is obvious that ESTAF has a significant potential to become an effective interface between ECVAM and the stakeholder communities represented in the forum.

Summary AISE (International Association for Soaps, Detergents and Maintenance Products)

- AISE has 37 members (national associations) in 42 countries. In total about 900 companies are organised in AISE.
- The agenda for sustainable cleaning (economic, social, and environmental) sets the framework under which AISE operates.
- Stakeholder dialogue is a key means in view of influencing and shaping the operation framework of the industries represented in AISE. This dialogue is rooted in technical and scientific aspects.
- Since 1999 AISE has started a series of voluntary initiatives in view of supporting the sustainable cleaning agenda.
- The potential contribution of AISE includes aspects of pre- and post-validation experience, the provision of reference materials/test items and laboratory support, input on regulatory options.

Summary CEFIC (Conseil Européen des Fédérations de l'Industrie Chimique; European Chemical Industry Council)

- CEFIC was described as the forum and voice of the chemical industry in Europe. CEFIC is committed to the 3R concept but is of the opinion that replacement is a long term goal when it comes to complex endpoints, thus stressing the need for short term solutions providing refinement and reduction.
- CEFIC engages in various research projects, prominently the CEFIC long range initiative (LRI), aiming to identify and fill gaps in understanding / assessing hazards of chemicals.
- CEFIC member companies operate routine testing facilities under GLP, performing studies with alternative methods as well as traditional animal studies. On the basis of these activities, member companies have considerable experience with regard to the potential relevance, practicability and use of new alternatives for the chemical sector.
- The potential contribution of CEFIC includes assessment of potential relevance, practicability and possible use of new test methods, and input on physical, chemical, toxicological properties of a wide variety of chemicals (that may be relevant for testing the performance of alternative methods).
- CEFIC expects that ESTAF be also a platform to share experiences and give advice/guidance on development and use of alternatives with the objective to progress alternatives in a pragmatic manner.

Summary COLIPA (European Cosmetic, Toiletry and Perfumery Association)

- COLIPA, the stakeholder organisation of the European Cosmetics Industry, stressed its efforts towards the development, optimisation and also validation (e.g. in collaboration with ECVAM) of alternative test methods. The 50 million euro joint commitment between the Commission and Colipa in the context of repeat-dose toxicity research was mentioned.
- COLIPA moreover maintains close interaction with other non-EU counterparts (US, Asia) on alternative approaches.
- One of COLIPA's key interests in the context of alternatives is to move towards a new testing paradigm, supporting the safety of cosmetics products.
- COLIPA's expectations were described as: increased transparency of stakeholder activities, progressing alternative methods in close dialogue with other stakeholders and helping ECVAM making decisions on the relevance of test methods for risk assessment.

Summary DGPT (Deutsche Gesellschaft für Experimentelle und Klinische Pharmakologie und Toxicologie)

- The German Society for Experimental and Clinical Pharmacology and Toxicology is a non-profit scientific society and is based on the association of 3 societies, among those the German Society for Toxicology. DGPT is part of the European Umbrella organisation Eurotox and has members from several EU Member States.
- DGPT promotes scientific and applied interests of pharmacology, clinical pharmacology and toxicology. It entertains a training programme in these disciplines. DGPT organises regularly scientific conferences, workshops, symposia. A major focus of DGPT's activities lies on the research and evaluation of alternative methods in these disciplines.
- DGPT could contribute to ECVAM's mission and ESTAF's roles through its scientific expertise on toxicology and alternative test methods.

Summary ECEAE (the European Coalition to End Animal Experiments)

- Formed in 1990, ECEAE is currently made up of 17 member organisations across 16 Member States.
- ECEAE is a registered stakeholder at the Member State Committee and the Risk Assessment Committee at the European Chemicals Agency, registered expert at OECD with other partners as International Council on Animal Protection at OECD (ICAPO), registered stakeholder at the European Medicines Agency (ICH/VICH) with other partners as International Council on Animal Protection in Pharmaceutical Programmes (ICAPPP).
- Aim is to peacefully campaign on behalf of animals in laboratories in view of a humane, modern science and a progressive legislation relevant for this area. Past successes include the campaining to ban cosmetics testing on animals in the EU and the provisions on the promotion of alternatives in REACH and Directive 2010/63/EC.
- Work is carried out by interacting with MEPs and officials to ensure that animals in laboratories are high on the European political agenda. ECEAE runs the "Humane Cosmetics Standard".
- Expectations and contributions to ESTAF include (a) Opportunity to be kept informed; (b) contributions to EVCAM activities and workshops, (c) support ECVAM relationships and effectiveness internationally; (d) opportunity to help promote and support ECVAM
- Suggestions for improvement directed at ECVAM's external presentation: (a) DB_ALM and ECVAM websites are not very user friendly or regularly updated; (b) Use of different websites (DB_ALM, TSAR, ECVAM) is confusing and does not give impression of a single centre; (c) Duplication of information on websites –validation status and acceptance; (e) Website works on frames- validation reports, statements, etc are not saveable nor the links themselves; (f) single

database of methods, easily searchable – by status- submitted, prevalidation, validation, acceptance

Summary ECETOC (European Centre for Ecotoxicology and Toxicology of Chemicals)

- ECETOC is a scientific, non-profit making, non-commercial association of companies active in the commercial areas of basic chemicals, speciality chemicals, pharmaceuticals, agribusiness, oil-related products, consumer products, food and beverages.
- At present (2011) ECETOC has 39 full member companies and 6 associate member companies.
- ECETOC provides a scientific forum through which extensive specialist expertise of manufacturers and users can be harnessed to research, evaluate, assess, and publish reviews on the ecotoxicology and toxicology of chemicals, biomaterials and pharmaceuticals.
- Currently ECETOC entertains 14 task forces addressing 10 Strategic Scientific Areas (SSAs). The latter are for instance reproductive health, integrated testing strategies, risk assessment of nanomaterials.
- ECETOC frequently organises workshops to get together scientists with the relevant expertise to support work of the SSAs and task forces. ECETOC also contributes to CEFIC's LRI (long range research initiative).

Summary ECOPA (European Consensus Platform for Alternatives)

- ECOPA is a pan-European umbrella association comprised of 'national consensus platforms' (NCPs) from 15 EU member states: Austria, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, the Netherlands, Norway, Poland, Spain, Sweden, Switzerland. ECOPA was previously represented on ESAC
- Quadripartite structure at EU & Member State levels comprising (1) academia, (2) animal welfare, (3) government, (4) industry. ECOPA works to achieve consensus among key 3Rs stakeholders to support & promote the 3Rs principle in the life sciences
- ECOPA has co/organised more than 20 high-profile conferences, consensus meetings & workshops promoting exchange of scientific information & high-level dialogue among stakeholders, reaching out to & engaging young scientists through ECOPA Science Initiative (eSI).
- ECOPA is currently received funding under the EU Research Framework Programmes for two 'specific supporting action projects': CONAM (Consensus Networking on Alternative Methods) and START-UP (Scientific and Technological Issues in Alternatives Research in Drug Development and Union Politics).
- ECOPA's expectations from ESTAF: (1) Enhanced dialogue among ECVAM & its stakeholders; (2) Opportunity for ecopa to continue its history of constructive engagement with ECVAM & key stakeholders
- ECOPA's contributions to ESTAF/ECVAM: Active dissemination via ECOPA website, newsletter, annual conferences and efficient engagement of 4 key stakeholder communities

Summary EFfCI (the European Federation for Cosmetic Ingredients)

- EFfCI member companies are manufacturers of cosmetic ingredients suppliers, and service providers to the cosmetics industry. Membership consists of ca 100 companies from all over Europe
- Activities include, inter alia, information on developments regarding alternative testing to raise awareness amongst members. Active participation in various industrial and regulatory Working Groups.

- EFfCI`s engagement is (a) to advocate the collective interests of all European cosmetic ingredient manufacturers and distributors; (b) to represent them vis-à-vis regulators (notably the European Commission) and the cosmetics industry; (c) to collaborate with authorities, cosmetic products manufacturers association, independent experts, and the media; (d) to constantly improve the safety of cosmetic raw materials for human health and the environment; (e) to improve the scientific basis concerning the development, validation and interpretation of alternative methods to animal testing
- EFfCI member companies encompass a broad spectrum of scientific and technical expertise concerning cosmetic raw materials. EFfCI can contribute in (a) providing reference data and practical experience in the use and testing of cosmetic raw materials; (b) adding expertise in industrial experimental toxicology concerning various toxicological endpoints; (c) promoting the use of alternative methods by providing members with concise and comprehensive information
- EFfCI's expectations from ESTAF: (a) constructive and focused cooperation concerning the establishment of scientifically justified definitions of the applicability domain of alternative methods; (b) the involvement in priority setting regarding test methods evaluation and validation to ensure practical relevance.

Summary EFPIA (the European Federation of Pharmaceutical Industries and Associations)

- EFPIA represents the research based pharmaceutical industry operating in Europe and has 31 national associations and 40 leading pharmaceutical companies as members. EFPIA is the voice within the EU of 2,200 companies in the pharmaceutical sector.
- EFPIA's mission is to promote pharmaceutical research & development and the best conditions in Europe for companies to develop new medicines to improve human health, including the industry's continuous quest for better therapies.
- EFPIA member companies are committed to applying the 3R principles, although the use of animals within state of the art testing strategies continues to be an essential part of the process of drug development and provides important safety information.
- EFPIA's possible contribution: The process of alternative method evaluation (especially in view of regulatory acceptance), should include the relevant industry experts having practical experience in product development, safety assessment and the relevant requirements. Based on the experience with validation, implementation and use of alternative methods, EFPIA wishes to contribute to the activities of ECVAM in all areas of nonclinical safety testing
- EFPIA expects that ESTAF will provide a forum for: (1) Open exchange among parties with commitment towards further development of 3Rs; (2) Consideration of practical aspects related to global development and realistic perception of hurdles during implementation of alternative methods; (3) Review of the experience with alternative methods following their validation (need for modification?)

Summary ESTIV (The European Society for Toxicology in Vitro)

- ESTIV has currently 232 individual members. Partner organisations are: Celltox (Italian Society for Toxicology In Vitro), INVITROM (Dutch-Belgium Society for In Vitro Methods, SCCT (Scandinavian Society for Cell Toxicology), IVTS (in vitro toxicology society, UK)
- ESTIV promotes the research and use of alternative methodologies, strengthens the scientific network of in vitro toxicologists, promotes in vitro toxicology both scientifically and educationally
- ESTIV achieves this by various activities including (a) connecting people; (b) advancing the science of *in vitro* toxicology; (c) encouraging education and training in *in vitro* toxicology; (d) establishing partnerships with other organisations and societies concerned with *in vitro*

toxicology; (e) facilitating communication between professionals in government, industry and academia to promote effective application of *in vitro* methods for hazard/risk assessment; (f) advocating scientific progress made in refinement, reduction, replacement, including *in vitro* toxicology.

- ESTIV recognises the essential role played by ECVAM in the pursuit of alternative techniques, by validating in vitro techniques and by providing an interface between the scientific community and the regulators.
- ESTIV's contributions to ESTAF/ECVAM may include: (a) Disseminating information via a regularly updated dedicated section on the ESTIV website, via newsletters and other internet channels, e.g. Linked-In and Facebook (to include summaries of the ESTAF meetings). (b) Encouraging feedback from the scientific community and provide updates at ESTAF meetings regarding feedback, opinions and comments (including the knock-on effect of identifying new expertise). (c) Organising meetings to bring together scientists with specific expertise, focusing on those areas where gaps currently exist. (d) Allocating time in the ESTIV conference program, for ECVAM scientific progress updates.

Summary EUPrim-Net (European Primate-Network (EUPRIM-Net)

- EUPRIM-Net links the European Primate Centres to form a Virtual European Primate Centre with the aim of supporting primate-based animal research that meets highest ethical standards. EUPRIM-Net achieves this through activities such as Best Practice / Education / Outreach / BioBank (of primate tissue) / research into Alternative Methods.
- Work package 10 of EUPRIM-Net is devoted to the development of *in vitro* technologies to replace, reduce and refine non-human primate studies. This research focuses on a few areas such as Central Nervous System (CNS) & Vaccine Research since these areas require at present a high number of in vivo studies, associated with often serious discomfort (invasive nature/long incubation periods in CNS research).
- Reg. CNS research current activities include (a) Development of in vitro model systems for the NHP CNS (Pre in vivo test phase), (b) Characterization of primary rhesus brain slice culture methods (c) Validation of primary in vitro glia cell cultures as pre in vivo screening method
- Reg. vaccine research, current activities include (a) Development of in vitro test methods for vaccine efficacy (b) Validation of ex vivo model for SIV vaccination efficacy (c) Development of in vitro test methods for discovery and refinement of adjuvants.
- Through participation in ESTAF, EUPRIM-Net expects to gain and exchange information on regulatory requirements and methods. EUPRIM-Net suggests that ESTAF may become a possible platform for the dissemination of solid information on alternative methods in primate research.

Summary Eurogroup for Animals

- Launched in 1980, Eurogroup is an umbrella organisation with 42 member organisations that comprise major European and international animal welfare organisations ultimately representing millions of European citizens. Eurogroup was represented in the original ESAC.
- Eurogroup strives to influence legislation to bring about improvements in view of its mission. Eurogroup acts a platform for its members to share knowledge and effective ideas/tools for campaigning.
- Activities include (a) advocacy (lobbying and campaigning) on EU laws, national laws or high industry standards; (b) monitoring the implementation of EU laws, (c) submission of complaints; (d) follow-up of legal, political, scientific, economic developments.

- Eurogroup is part of about ten advisory committees at five different Directorates General of the European Commission. Eurogroup also works with EFSA, ECVAM, EPAA, CAAT-EU, ICAPO and World Animal Health organisation (OIE). Eurogroup works with legislators, experts and industry towards the introduction, implementation and enforcement of EU laws in the area of animal welfare and in view of alternative methods to replace animal testing.
- Eurogroup works with Members of the European Parliament (MEPs) to support welfare demands (e.g. observes discussions in various parliamentary committees; supplies MEPs with information; has for 25 years run the Secretariat of the European Parliament's Intergroup on the Welfare and Conservation of Animals). Eurogroup also lobbies at Council level, informing successive EU presidencies about key welfare issues.
- Possible contribution to ESTAF/ECVAM: active participation in the promotion, development, validation, implementation and use of alternative methods in the EU and at an international level (large network of experts in member organisations)
- Expectations from ESTAF: The formation of ESTAF should (a) improve transparency of ECVAM's work (b) support the improvement of the promotion of the use of alternatives with scientists and regulators at the EU and international level. (c) ESTAF should play a role with regard to the transposition of the new Directive 2010/63/EU (awareness of national authorities in view of 3Rs concept).

Summary HSI (Humane Society International)

- HSI is a large animal protection NGOs in the world with about 11 million members globally. HSI has offices in UK, Australia, Canada, China, India, Latin America, USA.
- Spheres of activity include: (a) Public & corporate policy, (b) education, (c) direct care & disaster response
- HSI's goals are to achieve, in the near-term, (a) reducing animal use across product sectors, (b) to advance to this end science including the analysis of animal models that did not provide relevant results for the human situation, (c) raising the policy bar by improving standards of animal care and enforcement across the board, redirecting funding from animal to non-animal research, making use of alternative methods a legal requirement worldwide.
- HSI's approach to this end: (a) 'Building partnerships for progress', (b) Science-driven lobbying & advocacy; (c) Representing the views of supporters during policy-making & legislative processes
- In relation to its policy agenda, HSI is working with EU Competent Authorities for REACH and Classification and Labeling, ECHA Risk Assessment Committee (representing Eurogroup), EPAA Mirror Group & 3Rs Platform, OECD test guidelines & various endpoint expert groups, ILSI/HESI TTC steering committees, ecopa board of directors, US EPA pesticide programme 21c tox work group and ESTAF.
- Expectations/contributions include (a) to be able to provide input into ECVAM/EU-RL activities & planning, both in regulatory toxicology area & new basic/applied research mandate; (b) to provide science-policy expertise & multi-sector/international perspectives as well as the dissemination to HSI supporters & via AltTox.org, AXLR8.

Summary IVTIP (In Vitro Testing Industrial Platform)

- IVTIP is an informal forum of 45 companies including test developers, CROs, SMEs and large companies (sectors: chemicals, cosmetics, consumer products and pharmaceuticals) interested in the use of in vitro testing for product, regulatory/safety testing or early decision-making in compound discovery/development. IVTIP members support the 3R's and actively endorse a 4th R: responsibility towards animals as well as towards the growing demand by society for better ways of assuring safety.

- IVTIP promotes the implementation and acceptance of replacement strategies by industry and regulatory authorities through specific key activities: (a) informing members about existing and future programmes, regulations and directives concerning animal experimentation and 3Rs strategies; (b) informing institutions of the European Commission of industrial experiences with current initiatives and guidelines, and the needs within industry for replacement strategies; (c) assuring dissemination of progress and knowledge, and transfer of state-of-the-art technology with industrial applicability to IVTIP members; (d) representing the members at relevant organisations e.g. ESTAF and EPAA for driving the implementation and acceptance of 3Rs approaches for regulatory/safety testing
- IVTIP organizes two annual meetings covering issues identified and selected by the IVTIP members. These informal discussion forums enable opportunity to network, discuss and ask questions. Given the diversity among the members, general and specific expertise and guidance can be sought and found from various scientific angles opening possibilities for new opportunities.

2 Session 2: Stakeholder input on relevance of test methods proposed for validation

Test Submission Case Studies

Brief presentations were made of each of four test submission case studies for which the ESTAF had received written information and a discussion was held after each one. When introducing the discussion, the Chair asked the participants to focus on the level of information provided in the case examples and to focus not on the current level of development of the assay or its potential development, but on the potential user relevance of the information the test method under consideration would provide, assuming that it functions as indicated by the test developer. This included relevance of that information for regulatory applications, but also other aspects such as impact on the 3Rs as listed in the ESTAF response template which had been distributed before the meeting.

The members appreciated that a view had to be taken on the basis of limited information at this stage (i.e. pre-submission). Nevertheless several were of the opinion that rather more information would be required to provide advice on the potential usefulness and relevance of a test method at this stage. It was pointed out that it was not always possible to separate scientific issues, such as the chemical set used during development/optimisation of a method, from an accurate appraisal (even of a potential) relevance for various applications. Other stakeholders also pointed out that for issues such as ethical considerations, rather detailed information on the test system and the protocol were necessary to allow assessing whether the method used, for instance, foetal calf serum or was dependent on antibodies (as diagnostic tool) produced in animals.

A brief discussion followed on this particular issue concerning the activities of some ESTAF representatives towards increased awareness of the "hidden" use of animal experimentation (i.e. for antibody production) for seemingly animal-free in vitro methodologies. A representative from DG ENV (responsible for the amended Directive 2010/63/EU) confirmed that antibody production in animals was now considered animal experimentation (in contrast to the previous situation). As a consequence of this discussion, ESTAF representatives requested to be provided with as much information as was available and appropriate in view of confidentiality issues etc.

Closing the session it was agreed that the four test methods case studies would be circulated to ESTAF after the meeting for user relevance appraisal and feedback (using the ESTAF response template, see also section 4). ECVAM would look into the possibility to share more detailed information with the ESTAF representatives but underlined that at the moment of presubmission the information is by definition limited.

3 Session 3: Use and application of the Cell Transformation Assay within Industry, CROs, academia: ECVAM request for stakeholder feedback.

Due to time constraints, this session was very short and will be followed-up by written procedure after the meeting. The intention is to learn about the current use of CTA assays in industry and academia, receive information about strengths and weaknesses of the assay and its possible limitations. Practical experience with using CTA results in risk assessment would be particularly useful.

One stakeholder representative, referring to the SHE variant of the CTA (using cells from Syrian Hamster Embryos = SHE), remarked that in his/her view the test is of questionable relevance because the cell populations were not properly characterised and because there were problems with the repeatability / reproducibility of this rather complex test method in the laboratory. He/she also indicated that there had been problems with the predictive relevance of the CTA.

ECVAM noted this input with interest but reminded that there is currently no other alternative test method available (and certainly no one with a similar substantial body of evidence from past testing) that allowed to test for both genotoxic and non-genotoxic carcinogens. Acknowledging that the test had, like all model systems, drawbacks, ECVAM pointed to the legislative pressure, for instance in the Cosmetics area, and stated that the CTAs were the only in vitro test methods currently available to possibly enable compliance with this legislation, most likely in combination with other information sources.

4 Session 4: ESTAF's operation

Due to time constraints, also this session was very short. ECVAM communicated

a) that the ESTAF response template (distributed before the meeting and made available as room printed room document for discussion) would be checked one more time by ECVAM and then distributed again after the meeting. The template shall allow ESTAF to communicate its feedback on user relevance on test methods proposed to ECVAM in a structured and consistent way to ECVAM. ESTAF members are invited to use it for the first test cases and to provide feed back on the template to the ESTAF functional mailbox (JRC-ECVAM-ESTAF@ec.europa.eu) and the ESTAF Coordinator.

b) ECVAM will give all ESTAF representatives author rights on the ESTAF CIRCA page, so that stakeholders can upload and share documents at any point in time on their sections of this hub.

In the brief discussion that followed, stakeholders suggested

a) that ECVAM should play a more active role in promoting the development, optimisation and use of alternative methods by taking again more leadership in workshops, showing more visibility at conferences and, in particular, by alerting the test developer/submitter community to specific gaps existing with respect to the alternative test methods available to address specific endpoints. One idea brought forward was to organise calls for the submission of test methods addressing a specific (urgent) (intermediate) endpoint. Such calls could be open for some time and ECVAM could advance the most promising submissions into validation. Such calls would also help to structure efforts within industry and to provide incentives to submit tests for validation within a given timeframe, thus – potentially – accelerating this initial step of systematic test method evaluation for routine use.

b) Stakeholders stressed that ESTAF meetings be held biannually to allow effective information exchange. ECVAM welcomed this proposal but indicated that this would need to be verified.

The meeting ended at 16:00.

Possible dates for the next meeting will be communicated as soon as possible.

Annex 1: Final Agenda and Actions

Agenda

Item	Time	Description	Presentation| Discussion | Decision
	9:00 – 9:15	Opening of ESTAF Meeting. Tour de table	
1	**9:15 – 10:00**	**Session 1 ESTAF – ECVAM's participatory approach to stakeholder involvement** • Presentation(s) ECVAM *ECVAM's mission, processes, advisory structure. Reasons for and role of ESTAF.*	Presentation | Discussion
	10:00 – 10:20	**COFFEE BREAK**	
	10:20 – 13:00	• Summary presentations of representatives: advocacy, motivation and possible contributions of stakeholders • Open discussion: Expectations of organisations participating in ESTAF, roles of ESTAF etc.	Presentation | Discussion
	13:00 – 13:45	**BUFFET LUNCH**	
2	**13:45 – 14:45**	**Session 2 Stakeholder input on relevance of test methods proposed for validation** Request from ECVAM concerning a relevant selection of presubmissions	Presentation | Discussion
3	**14:45 - 15:15**	**Session 3 Use and applications of the Cell Transformation Assay for Carcinogenicity Testing within industry, CRO's, academia: ECVAM request for stakeholder feedback**	Presentation | Discussion
	15:15 – 15:35	**COFFEE BREAK**	
4	**15:35 – 15:50**	**Session 4 ESTAF's operation** • ECVAM proposal and open discussion	Presentation | Discussion | **Agreement**
5	**15:50 - 16:00**	Wrap up and closure of the meeting	

Actions

Item Nr.	Description	Required Activity & Timeline	Responsible for action
1	Distribution of ESTAF response template	Update of template as appropriate; asap	ECVAM
2	Distribution of four test methods for input on stakeholder relevance	Update of test method descriptions in view of more details; asap	ECVAM
3	CIRCA –BC follow up	Registration of all members and organisation of the site	ECVAM and ESTAF representatives
4	Request for information on the use of the Cell Transformation Assays (CTAs) for carcinogenicity testing within industry (i.e. for screening? for regulatory dossiers? For research?	By written procedure	ECVAM - feedback from stakeholders

ANNEX 2: Summary of parts 1, 2 and 4 of the introductory presentation by ECVAM

Background to ECVAM

ECVAM was originally set up in 1991 through a Communication from the Commission to the Council and the European Parliament pointing to a requirement of validating alternatives to animal testing as outlined in the original Commission Directive 86/609. ECVAM's roles and responsibilities were outlined in this Communication and the establishment of an Advisory Committee (the ESAC) was stipulated. In 2010 the Commission Directive has undergone revision (now Directive 2010/63/EU) and the JRC/ECVAM has been named as EU Reference Laboratory for Alternative Methods.

Mission of ECVAM

ECVAM provided an overview of ECVAM's role and tasks particularly in the light of the new Directive 2010/63/EU which lists tasks and responsibilities of ECVAM as EU Reference Laboratory in Annex VII. These tasks have been largely taken over from the previous Commission Communication first establishing ECVAM, with an additional requirement to promote the development and use of alternative procedures in the areas of basic and applied research as well as regulatory testing.

ECVAM's primary mission is to support EU policies in the field of consumer, environmental and animal protection by validating alternative methods for routine testing (mainly for toxicological hazard / risk assessments). Such methods should address the 3Rs, i.e. either replace, or reduce or refine the use of animals, whilst providing, on their own or in combination, the same or a better basis for risk assessment as current animal based methods. ECVAM shall also promote the development and use of alternative methods, including in basic and applied research and for regulatory purposes.

Current organisation

ECVAM's activities can be described as relating to validation, innovation and communicatio. With respect to **validation**, ECVAM's main role is the coordination of validation studies, the coordination of independent peer review of validation studies by ESAC, maintaining dialogue with stakeholders and experts before, during and after validation (including PARERE, ESTAF, and ICATM), the continuous development of validation criteria and support of post-validation activities, in particular those supporting the regulatory acceptance process.

Under **innovation** the development and optimisation of methods is included. The work will particularly adopt a multi-disciplinary approach combining *in vitro, in silico* and *omics* approaches, and focusing on improved mechanistic understanding (biological relevance) to address complex endpoints.

Communication promotes the use of alternative methods through their dissemination via the DBALM database, by providing a tracking tool on the progress of alternative methods through test submission to regulatory acceptance (called "TSAR") and by promoting dialogue with all relevant stakeholders, in addition to the PARERE and ESTAF networks.