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JOINT RESEARCH CENTRE

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

ECVAM SCIENTIFIC ADVISORY COMMITTEE (ESAC)

35th Meeting of the ESAC
4 – 5 October 2011
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Minutes

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Contents

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Participants

Present:

1. ESAC Members: David Basketter (ESAC Chair), Walter Pfaller (Vice Chair), Nathalie Alépée, Neil Carmichael, Jacques Chretien, Lucio Costa, Rodger Curren, Dagmar Jírova, Andrea Seiler, Erwin Roggen, Vera Rogiers (day 1 only), Kristin Schirmer, Ruud Woutersen (day 1 only).

2. Commission staff: JRC: Joachim Kreysa (HoU IVM), Maurice Whelan (HoU ST), Claudius Griesinger (ESAC Scientific Secretary), Sharon Munn, Juan Riego Sintes, Valérie Zuang, Sandra Coecke, Maria Pilar Prieto Pereita, Silvia Casati, Raffaella Corvi, Elisabeth Berggren, Susanne Belz, Alexandre Angers, Anita Tuomainen, ENV: Susanna Louhimies, ENTR: Michel Bouvier d'Yvoire, SANCO: Federica di Gaetano.

3. Observers: William Stokes (NICEATM), Jodie Kulpa-Eddy (ICCVAM chair), Hajime Kojima (JaCVAM), Yuko Sekino (National Institute of Health Sciences, NIHS, head of division of pharmacology).

Apologies:

1. ESAC Members: Coenraad Hendriksen, Wallace Hayes

2. Commission staff: JRC: Elke Anklam (Director IHCP), Annett Roi, Susanne Bremer-Hoffmann, SANCO: Karin Kilian, Susanne Hoeke, RTD: Arnd Hoeveler, Jürgen Büsing

3. Observers: Laurence Musset (OECD), David Blakey (Health Canada), Soon Young Han (KoCVAM).

Opening, conflicts of interest and administrative issues

Conflicts of interest

The Chair requested whether any ESAC member had specific conflicts of interest regarding any of the agenda points of this meeting and apart from the conflicts of interest already stated during the previous meeting (ESAC 34).

No new conflicts of interests were declared. It was agreed that the conflicts of interests formally declared during ESAC 34 (archived on ESAC CIRCA) would be regarded as maintained for the entire duration of the relevant review projects.

Actions from the last meeting

The Secretariat reviewed the actions of ESAC 34 which had all been addressed and completed except from the minor action of preparing a set of slides for the ESAC Chair which could be used at workshops and conferences to outlined ESAC's composition, role and modus operandi.

Administrative issues: e-mail communication and meeting registration

The Chair briefly raised two issues concerning the commitment of ESAC members with regard to the proper functioning of the ESAC: messages from ECVAM/ESAC Secretariat should be read carefully as they may contain important information either concerning review projects or logistical arrangements in view of plenary meetings. On the latter issue, the ESAC members were kindly requested to register as early as feasible in the online Commission/JRC meeting management system, specifying their flight details so that the logistics of transport and hotel accommodation could be properly organised. Since the JRC is receiving a large number of experts every day, taxi transportation needed to be booked well in advance.

1 Agenda point 1: ESAC review of the ECVAM follow-up study of the 3T3 NRU assay

Recapitulation of objective and questions of the review by the Secretariat

The Secretariat provided a short presentation on major characteristics of this study and, on the basis of these, reviewed the objective and questions that had been put forward to ESAC and its WG for review.

Presentation	File name
Hallmark of study and review of objective and questions put forward to ESAC	AP 1) 3T3 NRU - ESAC SEC.ppt

Briefly the hallmarks were:

(a) The test provides a binary classification (non-classified vs positive without further resolution of acute toxicity class),

(b) The test method as assessed in the present study uses only one of the binary classifications, namely 'Test Outcome Negative' (=TON) with regard to making predictions.

(c) Calculations of the proportion of TON out of all test results (=chemicals) on the basis of the accuracy values of the test method and assuming various prevalences of negatives were shown. The TON rate (if testing chemicals within the AD of the test) is still about 25%, even when assuming a prevalence of negatives of only 50%.

(d) Based on the considerations of the mechanistic basis of the test (basal = "general" cytotoxicity) and the absence of specific modes of actions (e.g. neuronal or cardiac receptors, channels etc.), the test had been suggested by ECVAM for use in a testing strategy and the review questions consequently took this into account.

(e) The review questions (as outlined in the ECVAM request for ESAC advice, ER 2011-02, adopted by ESAC in April 2011) in brief were:

1) Design and conduct of study – were these appropriate?

2) Conclusions of study – were these justified on the basis of the information generated and taking study objective (i.e. possible use of assay within testing strategy) into account?

3) Suggested use of test method according to Validation Management Group– were these plausible when considering the information generated in the study and taking into account relevant existing information?

Presentation by the Chair of the WG of the main findings of the ESAC WG responding to the review questions

Presentation	File name
Observations of ESAC WG reg. the study and main findings of the WG responding to the review questions	AP 1) ESAC WG-main findings.ppt

Following the recapitulation of the review questions and their rationale as captured in the ECVAM request for ESAC advice, the Chair of the ESAC presented the cornerstone observations of the ESAC WG regarding the test definition, the study design/conduct and presented the main findings of the review with respect to the three main review questions as outlined above.

Study design / conduct

In brief, the ESAC WG observed that the test method protocol and prediction model had undergone previous validation by NICEATM-ECVAM for another purpose and that the current study had aimed at assessing specifically the predictive capacity for identifying negatives, i.e. substances with an LD_{50} > 2000 mg/kg body weight.

The WG observed that the study had been designed and conducted appropriately in view of the objective, although some shortcomings with regard, in particular, chemical selection had been observed (i.e. restrictive exclusion criteria that possibly led to a small available pool of highly toxic substances). Moreover, the WG had remarks on how reference LD_{50} values had been derived for assessing the predictive capacity of the in vitro test method: the WG had for example concerns about using average LD50 values when the numbers were greatly different. The WG reported that in its view the study had been appropriately conducted to generate the information required to address the objective. The WG remarked positively on the practice of censoring and excluding values, alerted however to the fact that due to this practice, the actual datasets had been reduced with regard to the number of chemicals tested (since data points of some substances had to be excluded). The WG concluded that this reduction of available data points could have anticipated and that the number of test substances should, ideally, have been larger to accommodate such foreseeable reductions.

The WG reported that the test method was apparently robust and amenable to simplification / automation as the 2 non-validated protocols used in the study (one manual simplified version and one version run on an automated platform at JRC) gave comparable results in comparison to those obtained with the previously validated protocol (NICEATM-ECVAM study).

Conclusions of the study

The WG agreed with the validation study report (VSR) with respect to the millimole regression model being apparently the most useful prediction model. The WG observed that, independent of the protocol used, the Sensitivity (True Positive Rate) of the millimole regression model was high: about 95%: Due to the high sensitivity, most Actual Positives (AP) are correctly identified (True Positives, TP), very few AP are False Negatives (FN).

The ESAC WG agreed with the conclusion of the VSR concerning the very good predictive capacity of the test method for the identification of negatives. However, the WG emphasised, that this high sensitivity held true only for the applicability domain established on the basis of (a) considerations of mechanism of action that are transparently laid out (substances with a purposefully designed mechanism of action exclude: pharmaceuticals, pesticides etc.) but moreover (b) based on the selection criteria applied when creating the testing set (some classes of substances without specific mechanisms of actions but containing potentially highly toxic substances had been excluded). In this context, the ESAC WG alerted however to the fact that, when historical validation data are considered (i.e. the previous NICEATM/ECVAM study), the applicability domain may be larger. This view was supported by ECVAM pointing out that, for a definition of the applicability domain of the test and its limitations, all the data generated with the 3T3/NRU should be considered. In particular it was mentioned that the 72 chemicals tested during the NICEATM/ECVAM validation study included a appreciable number of pharmaceuticals and

pesticides and that, when a LD50 cut-off value of 2000 mg/kg b.w. is applied to these data, only "digoxin" is predicted as a false negative.

The ESAC WG agreed with the calculation as presented in the VSR (and based on the sensitivity of the test method as established by the validations study) regarding the potential percentage of chemicals (=TON) identified as negative by the 3T3 test method when assuming a prevalence of 87%, but remarked that the scenario offered dependent not only on the prevalence (assumed 87% based on an ECVAM analysis of the New Chemicals Database) but was also subject to applicability domain considerations not taken into account so far.

The WG disagreed with the VSR report with respect to the use of the Negative Predictive Value as a stand-alone measure of test performance. The WG remarked that such use was inadequate since being based on the specific composition of the testing set, including prevalence of negatives versus positives (the latter comprising four classes of acute oral toxicity).

The WG agreed with the limited applicability domain of the test method as outlined in the VSR. However, this particular issue led to some concerns of WG with regard to the test method being readily usable, even when incorporated in testing strategy (below).

Possible use of the study

While the ESAC WG agreed with the VSR conclusion that the test method would have to be used within a testing strategy due to the limited applicability domain of the test method, the ESAC WG had concerns regarding the immediate feasibility due to the absence of a possible and agreed conceptual framework of such a strategy and, in particular, due to the practical difficulty of defining

(a) exclusion criteria for chemicals that should not be tested in the 3T3 assay (or whose data, if tested, should be treated with caution) and

(b) possible tools for generating information / data to satisfy such criteria.

The WG felt that this issue was related to some shortcomings concerning the chemicals selected as testing set for the purpose of the study (i.e. the exclusion of particular classes from the validation set, including classes with some likelihood of highly toxic substances). The WG suggested that the study could have addressed the issue of AD in a better way by including some of these substances / substance classes (e.g. mutagens). It was confirmed by ECVAM that mutagens/carcinogens and so on had been excluded due to health and safety considerations concerning the participating laboratories.

Discussion of the WG results by the ESAC plenary in view of forming a consensus view on the study necessary for drafting an ESAC opinion on the validation study

It followed a discussion on the observations of the ESAC WG and the conclusions of the validation study as presented in the validation study report.

One ESAC member raised concerns with regard to a phrase used in the validation study report but also the ESAC WG report concerning (no citation) overpredictions of non-classified (NC) substances as being toxic. The member raised the issue that these substances were indeed toxic (cytotoxic) and that the correct phrasing would rather be to qualify such predictions as overpredictions of NC substances as being acutely toxic.

There was an extensive debate on the mechanistic basis of the test method, i.e. the absence of some more specific pathways of acute toxicity. While there was agreement that the variety of mechanisms potentially contributing to acute oral toxicity was much wider than basal cytotoxicity and that the test method (as specified in validation study report) addresses only a specific applicability domain (excluding molecules purposefully designed to activate specific mechanisms not present in 3T3 cells), some ESAC members pointed out that there are indications that basal cytotoxicity may in many cases be in fact more relevant for acute toxicity than the specific mechanism and, from a perspective of potency, even override the more specific mechanism.

ESAC members agreed that the practical use of the test may be challenging due to the applicability domain. While some substances [i.e. designed for oral uptake and acting via a specific mechanism of action (pharmaceuticals) and acting via a specific mechanism and likely to be (at least in background doses) ingested (pesticides)] could be easily excluded from testing also in the context of a practical application of the test, this would be more difficult for some substances (e.g. complex organics) that may contain functional groups that may activate specific pathways but may not have been designed to do so.

Caution was however introduced regarding this caveat by one ESAC member who stated that whether or not the test would work for such chemicals was simply not known at present, this did not mean that it would not also provide relevant results based on an assessment of basal/general cytotoxicity. Furthermore there was discussion that the issue of extrapolating on a probable applicability domain on the basis of a limited testing set during validation was a general difficulty of any (validation) study and not specific to this study. There was a brief discussion by the ESAC on possible ways to generate further data on more chemicals. ESAC recommended that ECVAM may consider expanding the current evidence on applicability, limitations and restrictions of the test by generating more data on test chemicals using the automated 3t3 NRU protocol that was validated during the present study.

The Secretariat summarised that, with regard to an ESAC opinion on the possible use, the main concerns of the ESAC related to (1) the limited applicability domain and the definition of appropriate restriction/exclusion criteria and (2) the assumption of a high prevalence of negatives (i.e. substances not requiring classification) as presented in the validation study report (assumed prevalence of 87% based on an analysis of the entries in the new chemicals database, NCD). As this value represents only chemicals that have passed the relevant tests from development over safety assessment to practical use (=registration in NCD), the Secretariat suggested that ECVAM could present this issue to its stakeholder forum (the ESTAF) in view of establishing what typical prevalences of negatives were in the early testing/screening phase, i.e. when this test may be most likely be used.

The NICATM observer alerted to the fact that the 3T3 assay including the SOP and prediction model are currently already in use within the regulatory context (OECD guidance document 129) for determining the starting dose and that some exclusion criteria with regard to the applicability have been included in guidance document 129. It was briefly discussed to which extent these criteria could be used for possible use of the 3T3 NRU methodology within a testing strategy for regulatory purposes, i.e. excluding substances (a) purposefully designed to act via a specific mechanism of action (e.g. pharmaceuticals, pesticides) and which are not represented in the 3T3 test system and/or (b) intended for oral uptake (pharmaceuticals) and/or (c) likely to be taken up accidentally via the oral route (pesticides). It was suggested by members of the ESAC that the test could hence be used for a variety of existing industrial chemicals not fulfilling above mentioned exclusion criteria. A relevant regulatory context could be the REACH legislation.

Further discussion touched on the use of confidence intervals of accuracy values (on the basis of validation study set) of the 3T3 validation study and for validation studies in general. There was agreement that CI should be used as is routinely done in other disciplines (e.g. validation / testing of diagnostic test methods in medicine), but that the meaning of CIs would need to be carefully explained in order to avoid misunderstandings, even more so as CIs so far have not been used when describing the accuracy of test methods following validation.

While it was acknowledged that the original papers reporting the LD50 values had not been accessed during the validation study and were hence not available to the ESAC WG and that it was therefore difficult to draw final conclusions on the quality of the reference data used, the ESAC acknowledged the difficulty of validating a test method for acute oral toxicity testing, considering the (generally observed) high intrinsic variability of reported LD_{50} results which are used as a gold standard against which the new test method is measured/validated. There was agreement however that there no other useful reference data were easily available, as, for instance, human data from accidental exposure are even more unreliable due the many sources of uncertainty related to the actual exposure levels etc.

Finally, ESAC agreed with the main findings of the ESAC WG, introducing minor amendments to the wording reg. the use of confidence intervals. It was agreed that the Secretariat, in collaboration with the ESAC Chair, would draft an ESAC opinion, taking the scientific discussion at the ESAC meeting into account, for adoption by written procedure.

2 Agenda point 2: Mandate of ESAC review concerning the Keratinosens study

Due to stated conflicts of interest of the ESAC Chair, this session was chaired by the ESAC Vice Chair.

This agenda point concerned the adoption of the ESAC mandate for peer review (objective, questions, timelines) as outlined in the relevant ESAC request. To this end ECVAM first summarised the design, results and conclusions of the external prevalidation study on the Keratinosens test method submitted by Givaudan. Following brief discussion of some technical issues of the study, the Secretariat presented a draft ESAC review mandate which was

adopted without further discussion. It was agreed that the final ESAC request containing the mandate would be circulated / uploaded on ESAC-CIRCA.

It followed a brief discussion on the usefulness of assessing reproducibility/variability on the basis of the raw data (in contrast to an analysis of the concordance of predictions yielded by applying the prediction model to the raw data). It was agreed that this may be useful in order to get a more basic understanding of variability of a test method, but that, to conclude on the sufficiency of reproducibility, acceptance criteria would have to be defined (just as for a concordance-based assessment). It was moreover agreed that more data should be requested from Givaudan to analyse data reproducibility and to allow for an extended analysis of predictive capacity (if available).

Presentation	File name
Presentation of Keratinosens submission on external prevalidation study	AP 2) KeratinoSens submission.ppt
Presentation of the ESAC review mandate (objective, questions, timelines)	AP 2) Keratinosens mandate.ppt

3 Agenda point 3: Presentation on the SEURAT-1 activity (repeated dose toxicity)

As had been requested by ESAC during the 34th plenary meeting in March 2011, ECVAM presented an update on the research activities of the SEURAT-1 cluster, the joint project of the European Commission and Colipa in view of replacing traditional in vivo repeated dose systemic toxicity testing (http://www.seurat-1.eu/). In brief the presentation outlined that

- The Cosmetics Directive foresees a ban on repeated-dose toxicity testing (RDTT) from 2013 onwards.
- Acknowledging the lack of scientific knowledge, methodologies and techniques to practically implement a replacement of traditional RDTT, DG RTD's health programme defined a long-range initiative: Safety Evaluation Ultimately Replacing Animal Testing (SEURAT).
- Funding (50 million) is shared to equal parts by Colipa and the European Commission.
- The Seurat-1 cluster operates via 6 projects (building blocks) addressing various scientific aspects of the problem. For details, see presentation.

It was agreed that ESAC members would receive the first book publication of the SEURAT-1 activity, describing the scientific progress, strategic developments and the evolution of the legislative and regulatory context to repeated dose toxicity testing.

Presentation	File name
Presentation of research activities of SEURAT-1 cluster aiming at the replacement of traditional in vivo repeated-dose toxicity testing	AP 3) Seurat-1_ESAC_Oct2011.ppt

4 Agenda point 4: ECVAM activity report

ECVAM presented the ongoing activities in its three pillars: validation, communication and innovation (basic and applied research).

Presentation	File name
Presentation of the validation and communication activities of ECVAM	AP 4) ECVAM-update-validation.communication.ppt
Presentation of the research activities of ECVAM	AP 4) ECVAM-update-innovation.ppt

With respect to the validation and communication activities the following main issues were presented:

- ECVAM is currently working on 10 validation studies concerning 14 test methods.
- A tentative schedule for the scientific peer review of these studies by ESAC showed that the review of these studies alone (without considering other that will come up in the mid-term) will most certainly extend over 2012 and 2013 and will result in an increased workload for ESAC.
- The successful setting-up of the ECVAM Stakeholder Forum (ESTAF) and the networks for the Preliminary Assessment of Regulatory Relevance (PARERE) was presented and some background provided to the results of the first consultation round concerning four test methods. The feedback received from ESTAF and PARERE was seen to be useful.
- ECVAM has, through adoption of the updated "Laboratory Animal" Directive, become a European Union Reference Laboratory. Ongoing implementation steps were briefly presented.
- With regard to incoming test submissions: ECVAM is currently evaluating 18 presubmissions and 11 complete submissions, relating to a wide range of health effects and health endpoints such as skin sensitisation, skin irritation, ocular toxicity, endocrine disruption, reproductive toxicity, acute toxicity, chronic toxicity, cardiotoxicity, neurotoxicity.
- The test submission assessment process was described which is to be followed by a prioritisation of submitted test methods. This prioritisation by ECVAM will take into account input on presubmissions from ESTAF, PARERE and ICATM. Initial ideas for prioritisation criteria were presented.

The projected tentative timelines for ESAC review projects were briefly discussed and it was agreed that timelines would be elaborated in more details for the various project and circulated as soon as available.

With respect to the innovation activities of ECVAM, the following main issues were presented:

- The innovation pillar of ECVAM (ST unit) is mainly involved in basic and applied research activities and supports to some extent also validation activities. The work addresses the following three areas: (1) mode-of-action and toxicity pathways, (2) high throughput screening (HTS) studies and (3) computational toxicology.
- The recent (September '11) joint workshop (JRC/Hamner Institute) on toxicity pathways was briefly presented. The WS addressed three basic questions: what is a toxicity pathway, how do we use toxicity pathways, what consequences will there be for safety assessment? (i.e. what consequences will the pathway concept, research etc. bear on the practice of risk assessment).
- The automation and high throughput testing of the Lumicell test method and the 3T3 NRU test method (under review during this ESAC meeting) were discussed in detail.
- Several scientific projects ongoing at present were briefly discussed, e.g. HepaRG model, mapping of chemical categories vs cellular effects (e.g. cell loss, mitochondrial damage, ROS intensity, Ca2+ efflux etc.), collaborative project with EPA on transcriptomics (based on the HepaRG test system).
- Finally, a brief overview of ECVAM's activities in computational toxicity, QSARs and biology-based modelling approaches was provided.

5 Agenda point 5 and 6: NICEATM/ICCVAM and JaCVAM activity reports

The NICEATM observer provided an update on its ongoing validation studies, peer reviews and recent test method recommendations in view of regulatory acceptance. The NICEATM-ICCVAM workshop on rabies vaccine potency testing was briefly presented. The involvement of NICEATM-ICCVAM in the Tox21 consortium and activities towards transformative research was highlighted.

Presentation	File name

Presentation by NICEATM-ICCVAM	AP 5) NICEATM.ICCVAM update(2).ppt

The JaCVAM observer (Dr. H. Kojima) communicated an important change with regard to the legal status of JaCVAM: In April 2011, JaCVAM became an official organization at the National Institute of Health Sciences (NIHS). The JaCVAM office is part of the Institute's division of pharmacology headed by Dr. Sekino (invited expert to this meeting). The JaCVAM steering committee has now become a full responsibility for JaCVAM's operations and output. The change of status will lead to a proper budget being allotted to JaCVAM (from the ministry of health, labor and welfare) and an increase in human resources for the evaluation of test methods as well as the coordination of validation studies and their scientific peer review. Additionally, JaCVAM's decisions with respect to alternative tests will be communicated as JaCVAM's official output to the department of the Ministry of Health, Labour and Welfare (WHLW) and publicly announced on the JaCVAM webite. This news was received very positively by ESAC and other representatives present.

Moreover, JaCVAM provided an update on its processes for validation, evaluation and peer review (in development) as well as information on past, ongoing and future studies. JaCVAM announced that the scientific peer review of the BHAS cell transformation assay (validated by JaCVAM) would be conducted as ICATM peer review by ECVAM's ESAC; ECVAM had already agreed to process the BHAS CTA through ESAC peer review.

Finally the JaCVAM observer emphasized the need for collaboration within the European Partnership for Alterantives to Animal Testing (EPAA), the Tox 21 project and to exchange information and opinions in the area of research and development of test methods. The observer highlighted that several projects are currently on-going in Japan on hazard assessment and test methods essential for the New Chemical Management Policy Ministry of Economy, Trade and Industry and another initiative is the Agri-Health Translational Research Project (Ministry of Agriculture, Forestry and Fisheries, Japan) and that input from the ICATM organizations on these projects would be welcome.

Presentation	File name
Presentation by JaCVAM	AP 6) JACVAM update.ppt

6 Wrap-up and actions

The meeting results were briefly summarised by the Chair (agreement on main points concerning the 3T3 NRU review, agreement on how to proceed with the draft ESAC opinion).

The VAM HuO (ECVAM validation pillar) introduced the necessity to update the ESAC Rules of Procedure (RoP) in view of introducing more stringent provisions to handle conflicts of interest. This had been requested by an internal JRC audit of the ECVAM activity and should include a paragraph in the RoP formally empowering the ESAC Chair to exclude members with conflicts of interests from the discussions, i.e. by asking them to leave the room.

The ESAC Secretariat briefly summarised the actions based on the discussions of the meeting:

Item Nr.	Description	Action / Timeline	Responsible for action
1	Preparation of draft ESAC opinion for adoption by written procedure.	By end November 2011	Secretariat and ESAC Chair
2	Proposal for next meeting dates 2013	By November 2011	ESAC Secretariat and Chair
3	Circulation of final ESAC request containing the mandate for peer review of the Keratinosens assay amongst ESAC and upload on ESAC CIRCA	Not specified	ESAC Secretariat

4	Request of additional Keratinosens data: (a) raw data to evaluate variability (b) additional data that may support this present evaluation	Not specified	ESAC Secretariat / ECVAM
5	Development of provisional timelines for the ESAC review projects in order to plan ESAC requests, setting up of ESAC WGs etc.	By November 2011	ESAC Secretariat in collaboration with the ESAC Chair
6	Update ESAC RoP in view of conflict of interest handling	Draft to be circulated in February 2012	ESAC Secretariat / ECVAM

Annex I – List of presentations

Nr.	Presentation on ESAC CIRCA	Presenter
Agenda Point 1 – ESAC scientific peer review of the 3T3 NRU assay		
1	AP 1) 3T3 NRU - ESAC SEC.ppt	ECVAM - Claudius Griesinger
2	AP 1) ESAC WG-main findings.ppt	ESAC - Neil Carmichael (Chair of ESAC WG)
Agenda Point 2 – ESAC scientific peer review of the Keratinosens test method		
3	AP 2) KeratinoSens submission.ppt	ECVAM - Silvia Casati
4	AP 2) Keratinosens mandate.ppt	ECVAM - Claudius Griesinger
Agenda Point 3 – Joint Commission-Colip research Project on Repeated Dose Toxicity Testing		
5	AP 3) Seurat-1_ESAC_Oct2011.ppt	ECVAM – Maurice Whelan
Agenda Point 4 – ECVAM activity report		
6	AP 4) ECVAM-update-validation.communication.ppt	ECVAM – Joachim Kreysa
7	AP 4) ECVAM-upcate-innovation.ppt	ECVAM – Maurice Whelan
Agenda Points 5 and 6 – NICEATM/ICCVAM and JaCVAM updates		
8	AP 5) NICEATM.ICCVAM update(2).ppt	NICEATM – Bill Stokes
9	AP 6) JACVAM update.ppt	JaCVAM – Hajime Kojima