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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)

34th Meeting of the ESAC

22 – 23 March 2011

EC JRC, Ispra, Italy

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Minutes

Minutes: Claudius Griesinger (ESAC Secretary)

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, Wallace Hayes, Dagmar Jírova, Andrea Seiler, Erwin Roggen, Vera Rogiers (day2 only), Kristin Schirmer, Ruud Woutersen.

2. Commission staff: JRC: Joachim Kreysa (HoU IVM), Maurice Whelan (HoU ST; participating only day 2), Claudius Griesinger (ESAC Scientific Secretary), Sharon Munn, Marlies Halder (only day 1), 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, ENV: Susanna Louhimies, ENTR: Michel Bouvier d'Yvoire, SANCO: Susanne Hoeke (participating only day 1).

3. Observers: Patric Amcoff (OECD test guidelines programme), William Stokes (NICEATM), Jodie Kulpa-Eddy (ICCVAM chair) participating in part by teleconference.

Apologies:

1. ESAC Members: Coenraad Hendriksen

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

3. Observers: David Blakey (Health Canada), Hajime Kojima (JaCVAM), Soon Young Han (KoCVAM).

1 Opening, conflicts of interest

The meeting was opened by the Chair, who suggested commemorating the victims of the earthquake and tsunami in Japan.

In the absence of comments from the ESAC, the agenda was adopted as circulated by the Secretariat.

The Chair requested whether any ESAC member had specific conflicts of interest regarding any of the agenda points of this meeting. Four ESAC members announced conflicts of interest concerning three of the agenda points to be discussed during ESAC 34. It was agreed that those ESAC members with specific conflicts of interest should summarise these forward them to the ESAC Secretariat to allow archiving this information on the ESAC-CIRCA electronic document repository and to support decisions concerning possible abstentions from reviewing or voting during adoption of final ESAC opinions concerning the specific projects.

- All four of these ESAC members had expressed potential conflicts of interests concerning the prevalidation study of three skin sensitisation assays, agenda point 5.
- Two of these four ESAC members expressed potential specific conflicts of interest concerning the definition of Performance Standards for the eye irritation assay (Cytosensor Microphysiometer, CM), agenda point 6.
- One of these four ESAC members expressed a potential conflict of interest concerning the follow-up study on the predictive capacity of the 3T3 NRU assay for acute oral toxicity testing, agenda point 8.

Based on the nature of involvement in relevant past activities (e.g. participation in ring trial) and the nature of the future work to be carried out (e.g. scientific review or definition of performance standards), the conflicts of interest were discussed as potentially prejudicial in view of participating in the relevant ESAC activity and ESAC decision making or not substantial enough to be expected to interfere with a neutral position when carrying out the work. Preliminary conclusions were reached on whether these conflicts were to be judged prejudicial for carrying out the requested projects:

> Agenda point 5 (Review of the sensitisation assays): For 3/4 of the ESAC members the stated conflicts of interest were considered potentially prejudicial in relation to a possible role of these ESAC members as peer reviewers of these assays and the respective ESAC members will not be able to participate actively in the review and the decision making (endorsement) of the ESAC opinion. One stated conflict of interest was considered not prejudicial with regard to a possible participation of the ESAC member in the review process.
>
> Agenda point 6 (Definition and review of performance standards for eye irritation assays): None of the stated conflicts of interest were judged prejudicial.
>
> Agenda point 8 (Review of the follow-up study on the 3T3 NRU assay): The stated conflict of interest was considered as potentially being perceived prejudicial. The ESAC member will neither participate in the review process nor the final endorsement of the ESAC opinion.

2 Actions from ESAC 33

The Secretariat reviewed the actions from the last meeting (ESAC 33, 12 October 2010). The only action to be addressed concerned the agreement of the Template for ESAC Opinions as already successfully used in the past CTA review. Minor adaptations of this template on the basis of the practical experience with this review were briefly presented and the template then adopted by the ESAC. Moreover, slightly adapted versions of the ECVAM to ESAC request template and the ESAC WG template (the reporting format for ESAC peer reviews of validation studies) will be uploaded on ESAC CIRCA. All relevant templates are available on ESAC-CIRCA (folder 3. ESAC TEMPLATES AND FORMS).

The Secretariat moreover provided a quick tour of the ESAC-CIRCA webpage, explaining how to use the document repository. It was agreed that the most important documents relating to upcoming ESAC meetings would be stored in a dedicated folder within the relevant meeting folder on CIRCA.

3 Feedback from the written procedure of the CTA study peer review

The process of the first scientific review of the renewed ESAC was discussed. This review had concerned the ECVAM-coordinated prevalidation study on 3 protocol variants of the Cell Transformation Assay (CTA).

The review process had nominally started after October 12 and the two relevant documents, ESAC WG peer review consensus report and ESAC Opinion were finalised by 18 February 2011. However, practically the review process had not started before December 14-16 when the 5 ESAC WG members met in Ispra for the kick-off meeting. Thus, considering the Christmas break, there was little more than 7 working weeks to finalise the review, find consensus in the ESAC WG as well as in the ESAC and agree on a final ESAC opinion. During this time the ESAC WG had held 6 teleconferences while the ESAC held 2 towards the end of the process when agreeing on the final ESAC opinion.

While the ESAC members expressed satisfaction with the review result (e.g. level of detail of the ESAC WG report and overall presentation of the ESAC opinion), there was general agreement that the timelines employed for the CTA were too tight to allow, under normal circumstances, a careful in-depth peer review to be conducted using external (=non Commission) expertise. The ESAC expressed concern about a possible repetition of a scientific peer review under such time pressure and ESAC members clearly indicated that such timelines must remain the exception in justified cases.

ESAC members also expressed the view that ESAC Draft Opinions should preferably be discussed in plenary meetings. The Secretariat agreed that this would be the ideal option, but highlighted that resorting to written procedure may also be necessary in the future. In the following discussion it was agreed that it was less the written procedure which ESAC members were concerned about, but the lack of appropriate time to review documents that had been revised and updated as the review progressed (ESAC WG report and Draft ESAC Opinion).

ESAC members involved in the CTA review expressed their appreciation of the support provided by the ESAC Secretariat (e.g. structure of the document and help with phrasing consensus text passages for issues that had been contentiously discussed by the ESAC WG/ESAC). It was indicated that this assistance from the Secretariat was provided on this occasion due to the extremely tight timelines of this review process, and should be seen as an exception. The IVM HoU took this opportunity to remind the ESAC that it was not the role of the ESAC Secretariat to pre-formulate possible ESAC opinions, but that ESAC members must take full responsibility for the phrasing of the ESAC Opinion.

In summary the following was agreed:

1. ESAC opinions should be discussed and endorsed preferably at plenary meetings. However, it is accepted that this will not always be possible due to possible delays during the review process (contentious issues, need to perform additional analysis – as was the case in the CTA review). Provisions for written procedure have been outlined in the ESAC rules of procedure also for such cases.
2. More importantly, the ESAC should have sufficient time to review updated documents (which again may necessitate finalisation by written procedure, albeit with more generous timelines).

4 Validation studies based on Performance Standards

To start the discussion on the issue of Performance Standards (PS), PS-based validations and the suggested ECVAM approach to peer review, ECVAM provided a presentation on the scientific and technical aspects of validation studies based on PS and a proposal on how to practically implement an efficient but rigorous process for ESAC peer review of PS-based validation studies. ECVAM furthermore presented an example of such an analysis on the basis of a me-too test submission for in vitro skin irritation testing, showing the assessment criteria for essential test method components (similarity) and how these had been used to decide on whether the proposed test method was sufficiently similar or not.

a) ECVAM's two-step approach to peer review of PS-based validation studies

With regard to the ESAC review process of PS-based validation studies, ECVAM proposed to dissect the peer review of such studies into two steps (Figure 1):

According to this scheme,

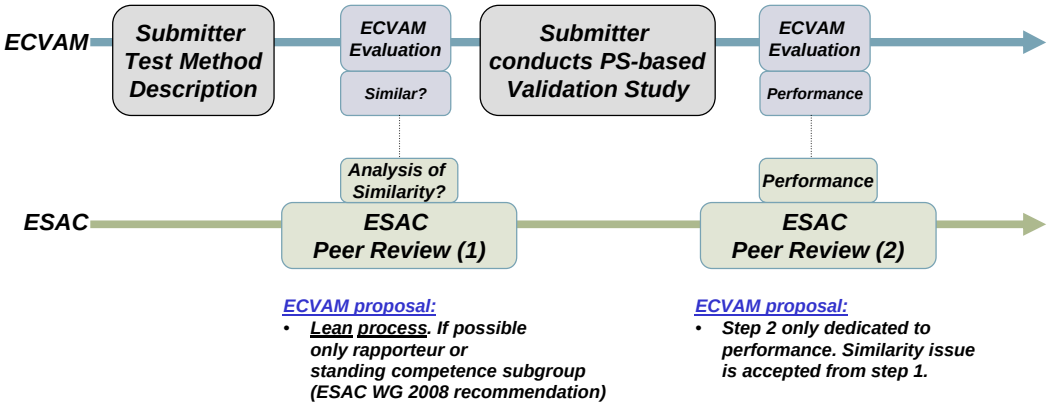
1. ECVAM would evaluate a test proposal from a submitter suggesting a PS-based validation study. This requires that test developers are made aware that ECVAM encourages and offers an independent evaluation of similarity prior to embarking on a small-scale PS-based validation study[1]. ECVAM would evaluate whether the test method fulfils the criteria of the PS necessary to qualify for such studies (i.e. sufficiently similar in relation to the validated reference method) and have this evaluation reviewed by ESAC in a lean, efficient and fast manner (i.e. written procedure with short timelines).
2. In case of a positive review (=confirmation of similarity), ECVAM would get back to the test developer confirming similarity and thus qualification of the test method for a PS-based study. The test developer could then organise the external PS-based ring trial (a small-scale validation study based on reference chemicals) and, after completion, submit the data on performance (accuracy based on the ref. chemicals) to ECVAM for evaluation and further review by ESAC. Importantly, similarity would normally not be reviewed again, unless the ring trial had generated further information questioning the information submitted at stage 1 concerning compliance of the methods with the essential test method components of the PS.

b) Reason for this approach

The proposal to dissect the peer review in two steps (1=similarity assessment, 2=performance assessment) was based on the observation that, in case of PS-based validations, two hypotheses need to be assessed/verified: 1) sufficient similarity and 2) equal performance. Similarity is a pre-condition for a test method to qualify of a PS-based validation study. Thus, were both hypotheses assessed/reviewed after completion of a PS-based study, there would be the possibility that either ECVAM assessment or peer review were unable to confirm similarity in this retrospective manner. In such cases the test method would not qualify for a small-scale PS-based validation study and that hence the ESAC peer review could not proceed with the review of test method performance in reference to the criteria laid out in the PS. In such a case, the test developer would have lost considerable amounts of time and money previously invested into a PS-based ring trial. To prevent such situations to occur, the peer review needs to confirm similarity before the inception of practical testing based on PS.

[1] In the updated ECVAM PS for in vitro skin irritation testing published in 2009, ECVAM has encouraged test submitters to submit a description of their test method to ECVAM for evaluation of similarity prior to embarking on a ring trial and submitting the complete study information to ECVAM.

Figure 1: ECVAM's approach to validation of similar methods follows a two-step approach consisting of an ECVAM evaluation of the test method proposal in particular in view of potential similarity and performance. These evaluations are paralleled by ESAC peer review of similarity and performance.



c) ESAC agreement concerning the two-step approach

>>> AGREEMENT 1 After discussing technical issues of similarity assessment, the ESAC agreed with the two-step review approach. Timelines for similarity review should be between one and two weeks (at maximum one month) and dealt with by written procedure, supported by teleconferencing if necessary.

Issues raised in this context of the discussion were:

- One ESAC member suggested that the first step of the ESAC peer review should only be performed in cases where ECVAM had not sufficient in-house expertise to judge similarity. The Secretariat pointed out that this would lead to an inconsistent approach, incompatible with the function of EC-JRC as a public body obliged to treat all test submitters/submissions in the same way.
- It was criticized by one ESAC member that only a small number of laboratories seemed to be involved in PS-based validation studies and other types of studies as well. It was questioned whether these labs were really inexperienced enough to qualify as 'naïve' labs (necessary for the assessment of transferability). ECVAM clarified that transferability assessment is not foreseen in PS-based validation trials. It was furthermore agreed that while laboratories participating in any sort of validation trial should be naïve with regard to the particular test method in question, they should not be "ignorant" with respect to the basic necessary techniques, i.e. sufficient expertise/knowledge about cell culturing, use of specific equipment etc.
- One ESAC member stressed that submissions for PS-based validations should not only furnish the necessary information in relation to the PS, but also additional background information on how the prediction model of the similar test method had been generated (e.g. number and nature of chemicals). ECVAM agreed that when evaluating a proposed catch-up validation study concerning a similar method and when preparing a dossier for possible peer review, background information was requested, in particular showing that the assay (SOP and prediction model) had not been optimised solely on the basis of the published reference chemicals, but also other substances.
- One ESAC member raised the point that the analysis of similarity always carried an element of expert judgement. ECVAM pointed out that for the judgement of similarity, the clarity of the pre-defined PS criteria was of key importance to allow a consistent and transparent approach. ECVAM emphasised that the right balance between rigidity and flexibility of criteria needs to be achieved when defining PS ("bamboo approach"). PS should not hamper the development of better/improved methods and therefore criteria should be flexible enough to accommodate possible scientific progress. In contrast, other criteria, especially those defining the actual nature of a given assay (its 'nuts and bolts') would need to be more rigid.

- One ESAC member inquired whether ECVAM would consider defining PS for the Cell Transformation Assay. The Secretariat explained that the finalised study had been a prevalidation study and was therefore unfit to serve as a basis for defining the PS for which considerable information on performance, applicability and limitations is required.
- In this context, ECVAM stated that it should be the standard approach of all validation organisations to define PS upon completion of a full pro- or retrospective validation study.
- In order to keep the terminology clear, one ESAC member suggested using "method similarity" instead of "similarity" when referring to the putative similarity of a new / updated test method in relation to a validated reference test method.
- DG ENV finally raised the point that ECVAM had now, with the revised Directive (2010/63) having entered into force, the legal possibility to lever fees for the evaluation of PS-based studies.

d) OECD's emerging concept of Performance-based Test Guidelines

Closing this session, the representative from the OECD test guidelines programme provided an overview of the recent developments towards the development of a new Test Guideline (TG) concept, termed Performance-Based Test Guideline (PBTG). The project was triggered by the observation that Test Guidelines should provide the information necessary to perform a given test method for generating data that fall under the OECD MAD agreement (MAD=mutual acceptance of data). However, a certain number of TGs contain Performance Standards as an annex. This may create the impression that data generated with methods that a developer or user may understand adhere to these standards (although not validated) would be covered by MAD, which is not the case. Moreover, with an increasing number of similar / me-too test methods expected (especially for building blocks investigating mechanisms of toxicity for the more complex health endpoints), OECD is looking for a logical way of creating an umbrella-type of TG which can be easily updated once me-too methods become validated. The central idea behind the PBTG concept is that the TG would be based on one or preferably more specific (validated) test method(s). However, the TG should not explicitly refer to these test methods. Rather, their essential test method components and performance characteristics should be identified/defined and used to describe the test method(ology) in the TG in a general way (hence "performance-based' test guideline = PBTG). Validated test methods adhering to this PBTG would then be annexed. The Performance Standards, necessary for validation, would in contrast be published as a separate document pointing to the PBTG. Moreover, supportive background documentation could be published separately but in reference to a specific PBTG, outlining more detailed scientific aspects of a specific methodology (an example is the ECVAM background document on in vitro skin irritation testing which was later published as an official OECD background document supporting OECD TG 439 on in vitro skin irritation).

5 Preparations for the ESAC peer review of in vitro skin sensitisation methods

This session (5) and the following session (6) were chaired by the ESAC Vice Chair since the ESAC Chair had expressed specific conflicts of interest concerning agenda point 5 (ESAC review of skin sensitisation studies).

Before the ESAC 34 meeting, on March 9, ECVAM had provided ESAC with a request for advice (peer review) concerning currently ongoing studies on four in vitro skin sensitisation test methods (ESAC request 2011-02.03). Two of these four methods are chemical reactivity assays measuring the key event of haptenation, while two other assays measure the activation of dendritic cells through the expression of appropriate protein markers on the cell surface. ECVAM had requested ESAC to set up an appropriate review structure (e.g. ESAC Working Group) composed of the necessary expertise to carry out a detailed review and report this to ESAC for final peer-review and adoption of an opinion. To compose this group ESAC should consider (a) proposals for suitable experts from ECVAM, (b) further proposals made by ESAC members following the meeting and (c) experts nominated by partner validation bodies collaborating with ECVAM under the ICATM Memorandum of Cooperation (ICATM=International Cooperation on Alternative Test Methods). The ESAC Secretariat had sent an invitation to nominate experts to ICATM partners on March 9.

ECVAM provided a presentation outlining the background to this request. Three of the four methods are currently undergoing validation of their reliability coordinated by ECVAM (the DPRA, the h-CLAT and the MUSST assays),

while one method is currently validated externally. The validation reports of the DPRA and the externally validated method are expected to be available by summer 2011. ECVAM presented the design and current state of the prevalidation study and information on the external study and proposed a list of possible experts that could act as ESAC WG members. Following discussion of the studies and scientific aspects of the tests (e.g. how many of the skin sensitisers do require metabolic activation and is metabolic activity therefore relevant?), the ESAC agreed to set-up a working group, chaired by an ESAC member (as stipulated by the ESAC Rules of Procedure). Following a suggestion by the Secretariat to discuss the expertise profile needed and then identify ESAC members and possible external contributors, the ESAC agreed that expertise in protein chemistry, immunology/antigen presentation, dendritic cell physiology as well as validation and statistics would be beneficial.

>>> AGREEMENT 2

ESAC agreed to set-up an ESAC WG for a detailed peer review of the skin sensitisation tests.

Considering the complexity of this endpoint and the fact that ultimately four test method studies will have to be reviewed, the ESAC WG could be composed of up to 8 members (including the ESAC members of the group).

Three ESAC members will serve in this group. One of the members will act as chair of the group. The final composition of the group will be agreed by ESAC through written procedure.

The final mandate of the ESAC WGs will be formulated by the core ESAC WG (=ESAC members of the group) in collaboration with the ESAC Chair and ESAC Secretariat and adopted by written procedure as soon as the final study reports are available.

It was furthermore agreed that the ESAC WG would be set-up according to the following steps coordinated by the Secretariat:

1) Justifications for expert proposals as basis for final ESAC decision making

All individuals/organisations suggesting possible experts should provide a brief justification/explanation as to why the expert is particularly suited to work in this group (background, expertise, participation in projects etc.). This input will be required for ESAC's final decision making concerning the composition of the WGs.

2) Creation of list with indications of preference for final decision by ESAC plenary

As soon as this information is available plus nominations/justifications from the ICATM organisations, a consolidated list will be prepared by the Secretariat for consideration by the ESAC. This list will contain proposals from (a) ESAC members, (b) ICATM, (c) ECVAM.

3) Decision by ESAC plenary

The ESAC will then decide on the final composition through written procedure.

4) Invitations and decision on date for kick-off meeting

Once the ESAC WG composition has been agreed by the ESAC, invitations will be sent to the experts, indicating possible meeting dates for a first meeting.

6 Definition of performance standards for in vitro eye irritation methods

Before the ESAC 34 meeting, on March 9, ECVAM had provided ESAC with a request for advice concerning the definition of Performance Standards (PS) for two ECVAM-validated in vitro eye irritation methods: the Cytosensor Microphysiometer (CM) assay and the Fluorescein Leakage (FL) assay (ESAC request 2011-01). PS for the CM would be urgently required in view of progressing the draft OECD TG on the CM which is blocked as long as PS are unavailable. ECVAM presented the ECVAM-coordinated retrospective validation study finalised in 2009 and the core findings of the ESAC review of that year. As had been outlined in the ESAC request 2011-01, ECVAM proposed the setting up of an ESAC WG to define PS for both the CM and the FL assays. The ESAC discussed the request and the following points were raised:

- It was questioned whether the assays and in particular the CM were really used on a routine basis at present. ECVAM pointed out that it was currently used in 2 laboratories worldwide, but that the intention of defining PS was precisely to create the basis for possible catch-up validation studies of putative similar test methods and to allow, as a first step (see agenda point 4) the evaluation and peer review of putative similarity on the basis of clear predefined criteria (essential test method components element of PS).
- The NICEATM/ICCVAM observer pointed to a possible difficulty in defining reference chemicals (element 2 of the PS): many of the test items evaluated in the retrospective study had been mixtures and these were not any more commercially available. Replying to this, ECVAM stressed that about 40 single substances (chemicals) were in the validation set which may be sufficient for composing a list of reference chemicals.
- No ESAC member felt comfortable chairing a possible ESAC WG for the definition of the PS for the CM. In the absence of volunteers, the ESAC Chair offered to fulfil this function. Following discussion of the necessary expertise for defining Performance Standards and an ECVAM proposal concerning how to proceed, the following was concluded:

>>> Conclusion

ECVAM informed the ESAC that it will prepare a proposal for the PS, with the help of an ECVAM expert group composed of ECVAM staff with the necessary expertise and additional external experts that are familiar with the particular test method. ESAC will be asked by ECVAM to peer review the draft PS.

Following up on the discussions, the Secretariat reminded ESAC members that the role of an ESAC WG chair is to coordinate the work of the group in collaboration with the Secretariat, to moderate the process in case of contentious issues and ensure the timely delivery of the ESAC WG report. It was pointed out that the ESAC Rules of Procedure clearly foresee that ESAC WGs are chaired by ESAC members and that it would be impossible for the relatively small number of ESAC members to have in-depth expertise on all possible toxicological issues that may be dealt with at the ESAC.

7 ESAC peer review of a follow-up study on the 3T3 NRU assay for acute oral toxicity

Before the ESAC 34 meeting, on March 9, ECVAM had provided ESAC with a request for scientific advice concerning the peer review of an ECVAM follow-up study on the predictive capacity of the already validated 3T3 NRU assay for acute oral toxicity testing (ESAC request 2011-02). ESAC was now requested to discuss how to review this study and, if deciding that an ESASC WG would be an appropriate structure, to discuss and decide on the composition of this group.

ECVAM presented the design and main results of this follow-up study. The study was designed to complement the information on predictive capacity of the 3T3 NRU assay for the specific purpose of identifying substances that do not need to be labelled for acute oral toxicity according to the EU CLP regulation (i.e. substances with LD50 doses above the limit dose of 2000 mg/kg body weight). The testing data of the validated protocol showed that the 3T3 NRU identifies true positives with a sensitivity of 94%. Since the 3T3 NRU is able to correctly identify most positives, negative test results in the 3T3 NRU are very likely to represent true negatives (non-classified chemicals) while positives carry a rather high likelihood to be false positives. In contrast the rate of false negatives is low. This is reflected by the high NPV (negative predictive value) of 92%. Therefore, the 3T3 NRU may be appropriate for identifying negatives as a first screening step in a tiered testing approach involving subsequent in vivo testing.

There followed a discussion on scientific and technical issues. These included

- One ESAC member inquired about the cost of this test. ECVAM explained that it was one of the cheapest tests available. It was furthermore amenable to automated approaches (automated testing had been conducted by IHCP/ECVAM in the context of the study) further reducing the cost of conducting the method.
- It was clarified that possible solubility problems of test items are addressed in a standardised manner: items are first dissolved in the culture medium (as vehicle). If they are found insoluble in the medium, they are dissolved in DMSO. If still insoluble, they are dissolved in ethanol. Solubility however can pose problems.

- The NICEATM observer inquired whether – in addition to the 2000mg/Kg b.w. threshold – also the 5000 mg/Kg b.w. had been assessed based on the testing data. ECVAM explained that this had indeed been done, but that the performance values derived when applying the 5000 mg threshold were poor (low specificity, low overall accuracy).
- One ESAC member raised concern that the test method, despite the high sensitivity and the resulting low rate of false negatives, might nevertheless misclassify possible highly toxic substances as not requiring labelling (i.e. not acutely toxic).
- ESAC members asked how well the applicability domain and possible limitations were known and inquired whether the test correctly identifies non-toxic substances of the use classes of (a) pharmaceuticals, (b) pesticides and (c) cosmetics. ECVAM clarified that the current study had not added much information on the applicability domain and that the relevant conclusions of the original ECVAM/ICCVAM validation study (finalised in 2006) were still valid in this respect. However, an obvious limitation was the lack of metabolic activity in the test system.

Following this discussion, the ESAC came to the following agreement with regard to the peer review process:

>>> AGREEMENT 3

ESAC agreed to set-up an ESAC WG for a peer review of the follow-up study on the predictive capacity of the 3T3 NRU assay.

ESAC agreed that the ESAC WG could be composed of up to 6 members (including the ESAC members to the group).

ESAC agreed on three ESAC members to serve in this group, one of these will act as chair of the group. The final composition of the group will be agreed by ESAC through written procedure.

The final mandate of the ESAC WGs will be formulated by the core ESAC WG (=ESAC members of the group) in collaboration with the ESAC Chair and ESAC Secretariat as soon as the final study reports are available.

It was furthermore agreed that the ESAC WG would be set-up according to the four steps as outlined under (5) and coordinated by the Secretariat.

8 Revised Directive for the protection of animals used for scientific purposes

DG ENV Unit D3 provided a summary of the changes of the revised Directive for the protection of animals used for scientific purposes (2010/63/EU). Key changes include that

(1) the 3Rs principle is now embedded in EU legislation and forms a cornerstone of the entire legislation extending to aspects of husbandry of laboratory animals etc. and

(2) the JRC (through ECVAM) has now been legally mandated to act as a European Reference Laboratory for the validation of alternative methods (whereas 47, article 48, annex VII).

9 Information from ICATM partners and OECD

Summary presentations were provided by two ICATM partners: ECVAM and NICEATM/ICCVAM outlined ongoing and future validation projects. ECVAM furthermore provided feedback from the Society of Toxicology Meeting (SOT) which had taken place in Washington at the beginning of March. ECVAM highlighted that US policy makers were increasingly willing to see alternative (non-animal) test methods to be introduced and that there was increasing momentum in the US towards the development of such tests, especially for identifying toxicity pathways. Moreover, the need for, and potential of mechanism-based tests to model identified modes of action was one of the key topics at the meeting. These developments, and the introduction of advanced tools such as "omics" into toxicology and toxicological testing provide challenges but also opportunities for the development and validation of alternative methods.

Further, the representative for the OECD test guidelines programme gave an overview over the current most important issues. It was in particular highlighted that the OECD test guidelines programme is about to start discussions on the revision of the OECD validation principles laid down in OECD Guidance Document 34. In the discussions that followed, ESAC appreciated the work of the different validation organisations and the OECD.

10 Synoptic table of agreements / conclusions reached

>>> AGREEMENT 1 – Validation / Peer review of validation studies based on Performance Standards

With regard to the validation and peer review of similar methods ('me-too' methods) the ESAC agreed with the two-step review proposed by ECVAM. Timelines for similarity review should be short and dealt with by written procedure, supported by teleconferencing if necessary.

>>> AGREEMENT 2 - ESAC Working Group for peer review of four in vitro sensitisation test methods

ESAC agreed to set-up an ESAC WG for a detailed peer review of the skin sensitisation tests. The ESAC WG could be composed of up to 8 members (including the ESAC members of the group). Three ESAC members will serve in this group. One of the members will act as chair of the group. The final composition of the group will be agreed by ESAC through written procedure. The final mandate of the ESAC WGs will be formulated by the core ESAC WG (=ESAC members of the group) in collaboration with the ESAC Chair and ESAC Secretariat and adopted by written procedure as soon as the final study reports are available.

>>> Conclusion – Performance Standards for Cytosensor/Microphysiometer

ECVAM informed the ESAC that it will prepare Performance Standards for the Cytosensor/Microphysiometer, with the help of an ECVAM expert group composed of ECVAM staff with the necessary expertise and additional external experts that are familiar with the particular test method and with the definition of Performance Standards. ESAC will be asked by ECVAM to peer review the draft PS.

>>> AGREEMENT 3 - ESAC Working Group for peer review of 3T3 NRU study

ESAC agreed to set-up an ESAC WG for a peer review of the follow-up study on the predictive capacity of the 3T3 NRU assay. ESAC agreed that the ESAC WG could be composed of up to 6 members (including the ESAC members to the group).

ESAC agreed on three ESAC members to serve in this group, one of these will act as chair of the group. The final composition of the group will be agreed by ESAC through written procedure.

The final mandate of the ESAC WGs will be formulated by the core ESAC WG (=ESAC members of the group) in collaboration with the ESAC Chair and ESAC Secretariat as soon as the final study reports are available.

11 Actions

Item Nr.	Description	Action / Timeline	Responsible for action
1	ESAC members with specific conflicts of interest to forward these in writing to the ESAC Secretariat	Preferably by 1 April	Four ESAC members with specific conflicts of interests and ESAC Secretariat.
2	Proposal for next meeting dates (2012 and 2013)	April 2011	ESAC Secretariat
3	Development of a set of slides for the ESAC outlining the composition, role, operation etc of the ESAC to be made available to ESAC members for presentations	Not specified	ESAC Secretariat
4	Setting up the ESAC WG for the review of skin sensitisation tests	As soon as all nominations and justifications for proposals are available.	ESAC Secretariat in collaboration with the ESAC Chair, Vice chair, ESAC WG chair and ESAC members of the ESAC WG
5	Setting up the ESAC WG for the review of the ECVAM follow-up study of the 3T3 NRU assay	As soon as all nominations and justifications for proposals are available.	ESAC Secretariat in collaboration with the ESAC Chair, Vice chair, ESAC WG chair and ESAC members of the ESAC WG
6	Distribution of ECVAM technical report on the Cosmetics deadline to ESAC (as soon as report is published)	May 2011	ESAC Secretariat
7	Distribution (via ESAC CIRCA) of the revised Directive 2010/63/EU	April 2011	ESAC Secretariat
8	Provide update on the Commission-Colipa project on repeated dose toxicity	Planning for October 4/5 2011 meeting.	ESAC Secretariat

Annex I – List of presentations

Nr.	Presentation on ESAC CIRCA	Presenter
Agenda Point 4 – Validation based on Performance Standards / PBTG concept		
1	AP4_ESAC34_General_PerformanceStandards.ppt	ECVAM - Claudius Griesinger
2	AP4_ESAC34_Similarity Assessment.ppt	ECVAM - Joao Barroso
3	AP4_ESAC34_OECD_PBTG concept.ppt	OECD - Patric Amcoff
Agenda Point 5 - ESAC request 2011-03/04: ESAC peer review of in vitro skin sensitisation assays		
4	AP5_ESAC34_Skin Sensitisation Test Methods.ppt	ECVAM - Silvia Casati
Agenda Point 6 - ESAC request 2011-01: Performance Standards for in vitro eye irritation assays		
5	AP6_ESAC34_Cell Based Assays.ppt	ECVAM – Joao Barroso
Agenda Point 8 – ESAC request 2011-02: ESAC peer review of follow-up study on acute oral toxicity assay		
6	AP8_ESAC34_3T3-NRU-follow-up-study.ppt	ECVAM – Maria del Pilar Prieto Peraita
Agenda Points 9 to 13: Activity reports and update on the revised EU Directive on the protection of animals used for scientific purposes		
7	AP9_ESAC34_ECVAM-update.ppt	ECVAM – Joachim Kreysa
8	AP10_ESAC34_NewDirective.pptx	DG ENV – Susanna Louhimies
9	AP12_ESAC34_NICEATM-ICCVAM-update.pptx	NICEATM – Bill Stokes
10	AP13_ESAC34_OECD-update.ppt	OECD – Patric Amcoff