



GUIDANCE DOCUMENT - ESAC PEER REVIEW

Organotypic *in vitro* assays to identify severe eye irritants – ICCVAM-NICEATM Retrospective Evaluation

March/April 2007

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I. Background information

European regulatory acceptance of the non validated tests

Major efforts undertaken by ECVAM and industry trade associations in the 90s, as well as historical confidence gained in-house led to the fact the usefulness of organotypic assays is currently well established within regulatory agencies and industry for specific and limited purposes although not formally validated. In particular, since July 2004 the EU Member States adopted the following common position (EC, 2004):

“Positive outcome from the following *in vitro* tests for eye irritation are acceptable:

- 1) isolated rabbit enucleated eye (REET, IRE) test,
- 2) isolated chicken eye (ICE) test,
- 3) bovine corneal opacity & permeability (BCOP) test,
- 4) hen’s egg test – chorio-allantoic membrane (HET-CAM) test.

Although these tests are not yet validated (and therefore not included in Annex V) it has been agreed¹ that available evidence is sufficient to conclude that the methods are able to detect severe eye irritants. Thus, where a positive result is obtained, a substance can be considered a severe eye irritant and R41 should be applied with no further testing justified, respecting animal welfare. Where a negative result is obtained, an *in vivo* test should subsequently be required, as the *in vitro* tests have not been shown to adequately discriminate between eye irritants and non-irritants. As

¹ 64th meeting of Competent Authorities (Copenhagen, November 2002) NOTIF/19/2002

with Annex V test methods, these *in vitro* tests should be conducted according to GLP where both the full test report (including basic data) and the study protocol should be made available”.

ICCVAM-NICEATM retrospective evaluation

In fall 2003, ICCVAM with the support of NICEATM initiated a retrospective evaluation of the BCOP, IRE, ICE and HET-CAM *in vitro* ocular toxicity test methods for determining their validity status for the identification of severe irritants and corrosives. For this purpose ICCVAM-NICEATM undertook the collection, compilation and evaluation of existing data in the form of Background Review Documents (BRDs), processed its review by an Expert Panel, and elaborated recommendations on the usefulness of the assays. The process can be summarised as follows:

- | | |
|----------|--|
| Fall 03 | Initiation of the retrospective evaluation |
| Nov 04 | Release of the Draft BRDs for Expert Panel Review and Public Comments |
| Jan 05 | Expert Panel Review meeting |
| March 05 | Expert Panel Review first report |
| July 05 | BRDs addendums according to Expert Panel recommendations and additional data collected |
| Nov 05 | Expert Panel Review final report |

Based on the expert panel recommendations, the BRDs and the public comments, ICCVAM has drafted recommendations on the four test methods. The final BRDs and their appendixes were available in August 2006, and the final ICCVAM recommendations were publicly available in Nov 2006.

ECVAM contributions

ECVAM has participated from the beginning of the process as liaison to the ICCVAM Ocular Toxicity Working Group (OTWG) which was in charge of steering the process of data collection and evaluation, but not in the formulation of the final ICCVAM recommendations. It contributed by providing:

- data from European validation studies,
- information on the European regulatory framework,
- formal comments based on the consultation of an ECVAM extended task force including experts on the test methods under evaluation, made on the draft BRDs (see attached document),
- internal comments from ECVAM on the draft Background Review Documents, on their addendums and on the draft ICCVAM recommendations.

References

EC (2004). Manual of Decisions for Implementation of the 6th and 7th Amendments to Directive 67/548/EEC on Dangerous Substances. Updated version of July 2004. 189pp. Ispra, Italy: European Chemicals Bureau, European Commission JRC. Website: http://ecb.jrc.it/DOCUMENTS/New-Chemicals/Manual_of_decisions.pdf.

II. Supporting documentation provided to the PRP

1. The ICCVAM Test Method Evaluation Report.

*Electronic link provided to PRP on 6 Nov 06, when available
(http://iccvam.niehs.nih.gov/methods/ocutox/ivocutox/ocu_tmer.htm).*

2. The supporting NICEATM Background Review Documents (BRDs) and their respective Appendixes on the four organotypic assays:

- Bovine Corneal Opacity and Permeability Test Method;
- Isolated Rabbit Eye Test;
- Hen's Egg Test – Chorioallantoic Membrane Test Method;
- Isolated Chicken Eye Test Method.

Paper copies provided to the PRP in Sept 06 following their availability in Aug 06.

3. ECVAM comments provided to ICCVAM made on the draft BRDs based on the consultation of an extended ECVAM Task Force on Eye Irritation.

Electronic file enclosed.

4. Hartung et al. (2004). A Modular Approach to the ECVAM Principles on Test Validity. ATLA 32, 467-472.

Electronic file enclosed.

III. Aspects considered in the evaluation by the ESAC peer review panel

Since the retrospective validation procedures applied for the organotypic assays have been already reviewed by an ICCVAM Expert Panel the ESAC PRP will represent a shadow group to review the previous peer-review process. The ESAC PRP agreed on evaluating the following points:

1. Consider if the ICCVAM material should allow a reasonable and expert person, for each of the test methods, to be satisfied that all of the relevant component parts of modular validation had or had not been properly addressed.
Consider also whether the proposed protocol and prediction model were adequate to attain the objective of the proposed test method.
The emphasis should be on 'positive reporting' - recording little against the headings where we find the required criteria have been met, and more where we have concerns they were not.
2. Consider if the ICCVAM processes were generally sound, that due process was followed, and due diligence exercised.
3. Consider if the ICCVAM comments and recommendations are supported by the evidence considered.
4. Advise if the ICCVAM comments and recommendations, constructed primarily in the context of the US regulatory environment, are applicable to the regulatory frameworks that apply within the EU.
5. Determine if there is any additional information not considered within the ICCVAM process, but which is required to inform ESAC's deliberations and outputs.
6. Consider if the ESAC PRP advice should be that ESAC endorses, or if (on the basis of scientific opinion and evidence) ESAC should offer modified or supplementary recommendations.
In addition, consider whether negative results could be used for regulatory purposes (e.g., R36 default classification).
7. General considerations: please address any other consideration you might have.
8. Conclusions and recommendation: please summarise your conclusions.
9. Evaluation report: the panel should provide a report addressing the above topics and any other important issues. The report should include a draft statement on the validity of the approach.

IV. Time for evaluation

See final timetable

Final timetable

| WHAT | WHEN | WHO |
|--|-----------------------------|-----------------------|
| (1) Circulation of dossier to peer review panel | done | ECVAM |
| (2) Preparation and circulation of proposed guidance for peer review | 20 March 07 | ECVAM |
| (3) Teleconference to agree procedures of peer review | 21 March 07 at 15.30 | PRP members |
| (4) Distribution of final agreed guidance document for peer review | 26 March 07 | PRP members and ECVAM |
| (5) Review of individual dossiers | by 12 April 07 | PRP members |
| (6) Teleconference to agree findings, conclusions and recommendation on validity of individual tests | 12 April 07 at 10.00 | PRP members |
| (7) Circulation of draft review dossiers on individual tests with copy to ECVAM | 12 to 24 April 07 | PRP members |
| (8) Teleconference to discuss and agree PRP overall conclusions and recommendations | 19 April 07 at 11.00 | PRP members |
| (9) Preparation and distribution of consolidated draft PRP report with copy to ECVAM | 24 April 07 | PRP members |
| (10) Circulation of agreed PRP report and draft of ESAC statement to ESAC members | 26 April 07 | ECVAM |
| (8) Finalise ESAC statement on scientific validity | 26-27 April 07 | ESAC / ECVAM |