ICCVAM Evaluation and Recommendations on the Nonradioactive LLNA: DA for Evaluating Allergic Contact Dermatitis Hazards

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Abstract

With increased need for nonradioactive techniques to evaluate skin sensitization, the National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (ICCVAM) evaluated the reduction and refinement benefits afforded by the LLNA compared to traditional guinea pig methods for ACD. This poster summarizes the ICCVAM evaluation and recommendations for the LLNA: DA.

Introduction

• A stimulation index (SI)
• The National Toxicology Program Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) analyzed accuracy of LLNA data.
• ICCVAM recommendations for the nonradioactive LLNA: DA are based upon concordance analysis of sensitizer/nonsensitizer results.
• Qualitative: Concordance analysis of sensitizer/nonsensitizer results.
• ICCVAM-recommended protocol formed the basis for the recently adopted OECD Test Guideline 442A.

Table 1. Concordance of LLNA: DA Tests Across Maximum SI Categories

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<td>100</td>
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<tr>
<td>Nonsensitizer</td>
<td>97</td>
<td>95</td>
<td>100</td>
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I CCVAM Recommendations: Test Method Usefulness and Limitations

• The LLNA: DA test protocol is based on ICCVAM-recommended protocol.
• The reduced LLNA: DA (rLLNA: DA) should be used routinely to determine the ACD hazard potential of test substances.
• The rLLNA: DA protocol uses only the high dose and reduces animal use by 40%.
• The rLLNA: DA protocol should be used for retesting non-sensitizers.
• The rLLNA: DA protocol should be used for retesting false negative test results.

I CCVAM Recommendations: Test Method Protocol

• The SI threshold for a positive LLNA: DA response (CV=36%), and 3.38% ± 0.79% (CV=23%), respectively.
• Like the reduced LLNA (Kimber et al. 2006; ESAC 2007; ICCVAM 2009a), the rLLNA: DA protocol may be employed
• ATP (adenosine triphosphate) content in draining auricular lymph nodes as an estimate of cell number at the end of the 48 hour incubation period.

I CCVAM Recommendations: Performance Standards

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I CCVAM Recommendations: Future Studies

• Efforts should be made to identify additional human data and experience for test substances to further validate the LLNA: DA.
• Additional nonsensitizing skin irritants should be tested to determine their impact on the LLNA: DA false negative rate.
• LLNA can be used to evaluate future ACD hazard potential of test substances.

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• OECD Test No. 442A: Skin Sensitization: Local Lymph Node Assay (OECD, 2010).
• OECD 2010. Test No. 442A: Skin Sensitization: Local Lymph Node Assay: DA, OECD Guidelines for the Testing of Chemicals, Section 4:

International Acceptance of LLNA: DA

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Figure 1. LLNA: DA Test Protocol

Figure 2. SI Decision Criteria Performance of the LLNA: DA Compared with the Traditional LLNA Using 44 Substances

Figure 3. Timeline for Evaluation of the LLNA: DA

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