ICCVAM Evaluation of the Local Lymph Node Assay (LLNA) for Potency Categorization of Chemicals Causing Allergic Contact Dermatitis in Humans

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ICCVAM evaluated the LLNA as a stand-alone test method to determine potency categorization of chemicals that may cause allergic contact dermatitis (i.e., potential skin sensitizers). The dose per unit skin area that induces a 5% positive response rate (i.e., DSA_{05}) in the human maximization test (HMT) or human repeat-insult patch test (HRIPT) was used as the human induction threshold. Substances with induction thresholds ≤500 µg/cm^2 were classified as "strong" human sensitizers. The extent to which the LLNA EC3 (estimated concentration needed to produce a stimulation index of 3, the threshold value for a positive response) correctly categorizes strong human sensitizers was evaluated by examining 136 substances with both LLNA and human data. Using EC3 ≤ 2%, a criterion recently adopted by the United Nations Globally Harmonized System of Classification and Labelling of Chemicals, correctly categorized 52% (14/27) of the strong human sensitizers. However, nearly half (48% [13/27]) of the strong human sensitizers had an EC3 > 2% (11/27) or were negative in the LLNA (2/27). Of the 11 strong human sensitizers with an EC3 > 2%, 91% (10/11) had an LLNA EC3 value between 2% and 10%. ICCVAM concludes that the LLNA can be used to categorize substances as strong sensitizers when EC3 ≤ 2% but cannot be used as a stand-alone assay to predict sensitization potency categories. Substances producing an LLNA EC3 between 2% and 10% will require additional information to determine that the substance should not be categorized as a strong sensitizer. To improve the accuracy of the LLNA for identifying strong sensitizers, ICCVAM encourages the development and evaluation of integrated decision strategies that consider other types of relevant information such as quantitative structure-activity relationships, structural alerts, peptide reactivity, *in vitro* testing data, human data or experience, and existing data from similar chemical entities.

Keywords: allergic contact dermatitis; skin sensitization; LLNA; potency; alternative methods; hazard categorization

Poster Session: Risk Assessment and Regulatory Policy Applications