Performance Characteristics of the Local Lymph Node Assay (LLNA) Limit Dose Procedure

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ICCVAM recommended the LLNA as a valid substitute for guinea pig tests for assessing allergic contact dermatitis in 1999. In 2007, the CPSC requested that NICEATM and ICCVAM evaluate the validation status of the LLNA limit dose approach, a modification proposed by Kimber et al. (Contact Dermatitis 54:181-185, 2006). In the limit dose procedure, only the high dose is tested compared to testing three or more doses in the standard LLNA. This modification reduces the number of mice used per study by 40% or more. Based on their retrospective evaluation of LLNA data for 211 chemicals, the LLNA limit dose approach, compared to the LLNA, had an accuracy of 98.6% (208/211), a false positive rate of 0% (0/42), and a false negative rate of 1.8% (3/169). Based on this publication, the ECVAM Scientific Advisory Committee (ESAC) concluded in April 2007 that the LLNA limit dose approach could be used to further reduce the number of animals used for skin sensitization testing. NICEATM subsequently obtained additional LLNA data on a total of 465 chemicals and formulations that were used to further evaluate the performance characteristics of the LLNA limit dose approach. Compared to the standard LLNA, the LLNA limit dose approach had an accuracy of 98.9% (460/465), a false positive rate of 0% (0/151), and a false negative rate of 1.6% (5/314). Similar to the three false negatives in Kimber et al., the 2 additional false negatives were classified as sensitizers in the standard LLNA based on the low- or middle dose producing an SI≥3, with the highest dose producing an SI<3. This evaluation of an expanded and more diverse group of chemicals supports the proposed use of the LLNA limit dose procedure. ILS staff supported by NIEHS contract N01-ES 35504.