Evaluation of the local lymph node assay using simultaneous confidence limits for ratio-to-control comparisons: Proof of hazard and proof of safety

Ludwig A. Hothorn[1]

[1] Institute of Biostatistics, Leibniz University of Hannover, Germany

The Local Lymph Node Assay (LLNA) provides an alternative method for identifying skin sensitising chemicals, standardized according to the OECD guideline No. 429. Cellularity or lymph node weight are assumed as a single, approximate normal distributed endpoint y_{ij}, measured on each animal j in a design including a negative control C and some doses D_i. A positive response is determined when the stimulation index $SI = \frac{\bar{y}_i}{\bar{y}_C}$ is larger than 1.5 in any of the doses according to Gerberick et al. 2007. Thus, a relative change is used as relevance criterion, analogously to the k-fold rule in the Ames assay. Compatible with such a relative relevance threshold, confidence limits for ratio-to-control comparisons are recommended. For the proof of hazard, lower confidence intervals are estimated which controls the familywise error rate, i.e. Dunnett-type approaches for ratio-to-control comparisons and which controls the comparisonwise error rate, i.e. pairwise contrasts. Because the limitation of the false decision rate is of primary interest in toxicology, alternatively a proof of safety is proposed, using simultaneous upper confidence limits. These three approaches are compared by means of a real data example. The computations of the confidence limits were performed by the R packages *pairwiseCI* and *mratios* according to Dilba et al. 2007.