

# **Dr David A Basketter, BSc, DSc, CBiol, FIBiol, FRCPath**

## **Comments on ICCVAM draft document on skin sensitisation potency**

1. A very considerable body of good work has been undertaken and well documented.
2. However, human data on skin sensitisation thresholds has been given undue status as an accurate gold standard. The threshold data (no effect/lowest effect) levels are actually subject to a number of problems. These are outlined below.
3. Human threshold data for an individual allergen often (perhaps the majority of the time) represents the result of a single determination, thus there is very little information on accuracy/reproducibility.
4. As a single determination, one has no idea whether a no/low effect level is close to, or far away from, the true human threshold.
5. The protocols used to generate these human threshold data points are distinctly variable, with clear evidence of differing sensitivities between tests, most notably when comparing the human repeated insult patch test (HRIPT) with the human maximisation test. The HRIPT itself is not a standard procedure, but rather a generic name for a class of test.
6. The protocols are not always fully described, thus assumptions have to be made about certain details, notably the dosimetry (including dose per unit area and time of application, both of which are important determinants of the sensitivity of the assay).
7. The human tests use a highly outbred species, further increasing the variability of these predictive assays.

All of these points are variously made in the publications which compare directly human predictive test and LLNA skin sensitisation thresholds, but I do not see this reflected adequately in the ICCVAM document. I suppose the key point is that LLNA EC3 values, as the document indicates, do show a correlation with human thresholds, but they cannot be expected to predict the historic human data with great accuracy because that historic data is not of itself particularly precise and certainly is very far from representing a gold standard. No amount of statistical/mathematical agonising will tell us more, we just have to live with it and recognise that the human data might be good enough to indicate there is a correlation, but is not good enough to inform us about the quality of that correlation.

Please do not hesitate to ask if you have any questions.

A handwritten signature in black ink, appearing to read 'D A Basketter', written in a cursive style.