Subject: New Form Results 2
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Below is the result of your feedback form. It was submitted by
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QuestionsComments: Questions from the OECD Expert Group on Sensitization

I. The approach by ICCVAM to validate the LLNA for the prediction of strong and weak skin sensitizers poses a methodological challenge. The reason is that the possibility of misclassification in humans of a substance˙s potency may negatively influence the outcome of the validation; i.e., it is possible that available HRIPT and HMT data may lead to a false human skin sensitization potency categorization. It is often difficult to correctly interpret the total dose used in the human tests due to insufficient documentation of total area dosed or possible prior patient exposure history.

In their analysis, Schneider and Akkan (2004) used the chemicals included in the 1999 ICCVAM validation as a starting point for a literature search to identify skin sensitizers for which quantitative human data on induction doses were available expressed as dose per unit area (ug/cm2). They were able to identify and assess 46 substances. They were not able to identify more substances as relevant uncertainties are related to limitations in the human data, which mostly come from older studies. First, the reporting of size of the skin area to which the test substance has been applied and of the volume of test solution used is often insufficient. In some cases, skin area and test solution volume could be deduced from information given on types of patches and application systems used. Moreover, in human HRIPT and HMT studies observed incidences for sensitization reactions depend on the concentrations applied

during both the induction and elicitation phase. Often, but not in all cases, the same concentration was applied for both phases. Otherwise, the overall outcome of the test may have been influenced by different elicitation concentrations, a factor not considered in the regression analysis.

In the evaluation performed by ICCVAM in 2008, 76 substances with quantitative human data among them 16 with negative LLNA results have been included. With respect to the points raised by Schneider and Akkan, it is important that it is described why it was possible in the current analysis to include more substances with both positive human and LLNA data (n=60) than Schneider and Akkan (n=46). Therefore, detailed information on ICCVAM˙s assessment of human dose per unit area is needed and the possibility of misclassification arising from such approach needs to be described. This is important with respect to the assessment of the rate of putative misclassification of strong/weak skin sensitizers using the human data in order to interpret the outcome of the validation study.

- Should the HMT and HRIPT data be treated as equivalent?
- Is a correction factor/uncertainty factor/safety factor of 10 the most appropriate for the extrapolation of LOAEL values to NOAEL values? Schneider & Akkan (2004) used arithmetic means for human and LLNA data except when there were discordant results with varying vehicles. The authors interpolated linearly from the LOEL to a dose corresponding to an estimated sensitization incidence of 5% (DSA05). Griem et al (2003) used LOAELs which were divided by an arbritary factor in cases of high observed incidences.
- ICCVAM analyzed 250 ug/cm2 and 500 ug/cm2 as the cut-off values for a stronger sensitizer. Has the reverse analysis been performed where the LLNA (e.g., at EC3 1% or 2%) and the GP data have been set as the standard and an optimal human cut-off calculated (does it vary between the LLNA and the GP data)?

II. Once criteria are determined for acceptability and use of human data, questions arise about the data from LLNA studies:

- Can the LLNA protocols be narrowed, e.g., by selection of solvents or choice of other test parameters to improve correlation coefficients? Is it meaningful to combine results for different solvents?
- For repeat LLNA studies for a chemical substance, which EC3 value should be selected? Should the geometric mean or the most conservative value be used?

III. How representative of sensitizers may the selection of chemicals with human data be? Does the set of chemicals analyzed by ICCVAM emphasize strong sensitizers?

IV. What are the differences between the validation approach used by Basketter, Gerberick and Kimber (BRD Appendix A) with the approach taken by ICCVAM?

V. With regard to Table 6-2, please compare and contrast the approaches taken by the various investigators represented. That is, analyze the possible sources of variability in the various approaches.

VI. Note that ICCVAM presents the variability among EC3 values for repeat LLNA tests. Can the panel estimate variability for human data points?

VII. When weighing evidence in human or animal data, what are the critical parameters to be considered?
