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Brussels, 20 December 2004

Dear Dr Stokes

This public comment is delivered in response to Federal Register Notice Volume 69, Number 212, Pages 64081-64082. It provides some overview comments from the European Cosmetic Toiletry and Perfumery Association Colipa on the Background Review Documents (BRDs) published on November 1, 2004 for the Bovine Corneal Opacity Test (BCOP), Isolated Chicken Eye Test (ICE), Isolated Rabbit Eye Test (IRE) and Hen's Egg Test - Chorioallantoic Membrane (HET-CAM).

Colipa very much welcomes the activity of ICCVAM to address *In Vitro* Test Methods For Detecting Ocular Corrosives and Severe Irritants. It is extremely impressive to see the tremendous work that has been done in this area especially as it relates to the effort it has taken to produce such comprehensive BRDs on BCOP, ICE, IRE and HET-CAM. ICCVAM is to be congratulated on this very important activity.

The BRDs are an excellent starting point for developing an action plan to make further progress with the possible validation of the four *in vitro* methods mentioned above for the detection of eye corrosives and severe eye irritants. As you are aware, Colipa has been and remains very active in the area of eye irritation both in terms of validation of *in vitro* methods and research on chemically-induced mechanisms of eye irritation. In light of this, we would like to offer the following general comments:

- We would welcome further clarity on the sources of data used in compiling these documents and whether all available sources of data have been incorporated e.g. IRAG submission data for eye irritation alternatives, 1993.
- We acknowledge the complexity of some of the protocols involved and recommend the need for additional work to examine further the relationship between the experimental protocols, prediction models and subsequent interpretation of the data e.g. differences in the HET-CAM protocol and prediction model used in the German HET-CAM validation study^{1,2} and the EC/HO validation study³.
- We acknowledge the possibility that the *in vivo* test will need to be replaced by more than one *in vitro* assay. We would welcome discussion on the choice of the statistical approaches that would be necessary to allow decision making from complex matrices of data.

- We believe that we are currently presented with a unique opportunity to use a weight of evidence approach to retrospectively validate alternative methods/strategies for eye irritation and identify future research and validation needs.
- Such retrospective analysis should allow us to identify further research needs on the mechanisms of chemically induced eye irritation e.g. the mechanisms involved in reversibility of injury are key to the prediction of eye corrosives and severe eye irritants.

With a view to establishing the timetable for phasing out animal testing for the purposes of the 7th Amendment of the EU Cosmetics Directive, the European Commission/ECVAM have recently co-ordinated a stakeholders report entitled "Report for Establishing the Timetable for phasing out animal testing for the purpose of the Cosmetics Directive"⁴. On the basis of the eye irritation expert conclusions within this report, it has been defined that the possibility of validating *in vitro* methods on the basis of existing data could lead to a full replacement of the *in vivo* eye irritation test by 2009. Colipa is firmly committed to being an active partner in helping to achieve the goals of validated animal alternative methods for eye irritation that use the best science possible, make most effective use of resources and seek to meet timelines where at all possible.

We shall be attending the expert panel meeting to be held on 11/12 January 2004 to provide our in-depth technical comments at that time on the BRDs for the four methods.

Yours sincerely



Bertil Heerink

¹Spielmann, H., Kalweit, S., Liebsch, M., Wirnsberger, T., Gerner, I., Bertram-Neis, E., Krauser, K., Kreiling, R., Miltenburger, G., Pape, W. & Steiling, W. (1993). Validation study of alternatives to the Draize eye irritation test in Germany: cytotoxicity testing and HET-CAM test with 136 industrial chemicals. *Toxicology In Vitro* **7**, 505-510.

²Spielmann, H., Liebsch, M., Kalweit, S., Moldenhauer, F., Wirnsberger, T., Holzhutter, H-G., Schneider, B., Glaser, S., Gerner, I., Pape, W.J.W., Kreiling, R., Krauser, K., Miltenburger, H.G., Steiling, W, Luepke, N.P., Muller, N., Kreuzer, H., Murmann, P., Spengler, J., Bertram-Neis, E., Siegemund, B. & Wiebel, F.J. (1996). Results of a validation study in Germany on two *in vitro* alternatives to the Draize eye irritation test, the HET-CAM test and the 3T3 NRU cytotoxicity test. *ATLA* **24**, 741-858.

³Balls, M., Botham, P.A., Bruner, L.H. & Spielmann, H. (1995). The EC/HO international validation study on alternatives to the Draize eye irritation test. *Toxicology In Vitro* **9**, 871-929.

⁴Web link: <http://pharmacos.eudra.org/F3/cosmetic/AnimalTest.htm>