Cosmetics Europe, Brussels, Belgium, 4th Oriel RAJ, Auryn France, 4;Janssen Research & Development, Beershe, Belgium, Henkel AG & Co. KGaA, Düsseldorf, Germany, 4;Chanel Parfums Beauté, Neuilly Sur Seine, France, 4;The Procter & Gamble Company, Egham, United Kingdom, 4;Institut de Recherche Pierre Fabre, Castres, France, 4;Beiersdorf AG, Hamburg, Germany, 4;LVMMH Recherche, St. Jean de Braye, France.

Introduction

Cosmetics Europe’s Task Force Eye Irritation (TFEI) is actively involved in the development of alternative methods to assess eye irritation potential of cosmetic ingredients using in vitro methods, based on optimizing current in vitro test methods, applied research projects and collaborative activities with external partners. Selecting chemicals for use in the development and evaluation of in vitro eye irritation assays based on a thorough understanding of what drives irritation in classification of ocular effects of chemicals in the in vivo rabbit Draize test is therefore a critical and essential element that enables identification and evaluation of predictive power and applicability domain at an early stage of development. To facilitate understanding of the importance of such drivers of irritation, Cosmetics Europe TFEI has undertaken an in-depth analysis of the publicly available external databases containing in vivo eye irritation data for 258 chemicals and solutions of chemicals tested in the Draize eye irritation test. This analysis is based on having good quality in vivo data that has allowed a clear understanding of the different ocular tissues effects that drive classification. These include corneal opacity (CO), iritis (IR), conjunctival redness (CR), conjunctival chemicals (CC), days to clear and/or persistence of effects. In addition, all 258 chemicals were screened for their commercial availability, assurance that they cover the whole range of irritation potential and represent relevant classes and physical states. Until today such an analysis is unprecedented, and it will have important implications for in vitro methods development, evaluation and validation activities.

Strategy for Building a Master Chemicals List

1. Collection of chemicals with good quality in vivo data from existing databases (e.g. ECETOC, ZEBET and Laboratory National de la Sante (Gautheron)) and generation of UN GHS classifications for eye irritation
2. Identification of the in vivo drivers of UN GHS classification, as depicted in Table 1
3. Differentiation of chemicals according to the drivers of classification as depicted in Table 2 and Figure 1, using the following prioritization scheme:
   a) Category 1:
      - Chemicals classified based on severity (mean scores of Days 1-3)
      - Chemicals classified on persistence at Day 21, but not severity
      - Chemicals classified based on CO > 4, but not severity or persistence
      - Choice of endpoint driving classification dependent on the number of animals
   b) Category 2:
      - Choice of endpoint driving classification dependent on the number of animals
   c) No Category:
      - CO = 0 chemicals showing CO scores equal to zero in all animals and all observed timepoints
      - CO > 0 chemicals showing at least one CO score higher than 0 at any timepoint in any animal

Table 1: List of the in vivo drivers of UN GHS classification

<table>
<thead>
<tr>
<th>Category</th>
<th>Hazard Score of Days 1-10</th>
<th>Hazard Score of Days 11-21</th>
<th>Category 1</th>
<th>Category 2A</th>
<th>Category 2B</th>
<th>Category 3</th>
<th>Category 4</th>
<th>Category 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>B</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>R</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>C</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>D</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Conclusion

Our analysis clearly demonstrates the importance of understanding the in vivo tissue effects which drive eye irritation classification according to the UN GHS system. This builds on recent good publications in this area (Atrißkows et al. Archives of Toxicology 2013). The availability of such a comprehensive list of the drivers of irritation for identified chemicals will be a critical and essential tool when selecting chemicals for development, evaluation and validation of new in vitro eye irritation tests. Valuable insights can be taken from our analysis of the Draize: 1) high involvement of corneal effects driving Cat 1, Cat 2A and Cat 2B classifications; 2) when persistence of effects at day 21 drives Cat 1 classification, this is primarily based on corneal effects; 3) the importance of corneal redness in classification of Cat 2A versus 2B; 4) The effects of this chemical on all tissues which drive classification. Also the physical form of the chemicals can have an impact e.g. many more solids than liquids are classified Cat 1 when based on the criterion of CO4; 5) The availability of such a comprehensive list of the drivers of irritation for identified chemicals which will be published in a peer-reviewed journal.