Using the LLNA to Categorize Strong Skin Sensitizers


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Abstract

Introduction

Allergic contact dermatitis (ACD) is one of the most common types of occupational disease. Because the prognosis of ACD is poor, prevention is important. According to the U.S. Bureau of Labor Statistics, allergic contact dermatitis (ACD) is one of the most common workplace diseases (BLS, 2018). Skin sensitization is an important cause of occupational disease with a relative low but substantial incidence of allergic contact dermatitis in relation to relatively high exposure. The GHS was revised in 2009 to include the option of further subdividing potential skin sensitizers into “strong” (1A) and “other” (1B) categories (GHS) includes criteria for classifying substances as skin sensitizers (which produce ACD) or skin irritants. The LLNA was a valid alternative to guinea pig test methods for many testing situations; however, it was not a valid alternative to sarcocyte test methods. Using the LLNA to categorize substances as strong sensitizers was proposed to be based on the LLNA EC3 value when LLNA EC3 > 2% as shown in Table 1.

Table 1: EC3 Categorization for Skin Sensitizers

<table>
<thead>
<tr>
<th>Sensitizer Type</th>
<th>EC3 Cutoff</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>&gt;2%</td>
</tr>
<tr>
<td>Other</td>
<td>≤2%</td>
</tr>
</tbody>
</table>

Methods

Human Test Method

Figure 1. A diagram showing the process of applying test substances. For each test subject, a patch is applied to their skin and left for a specified time. Following this, the patch is removed and the skin is observed for signs of irritation. If irritation is present, the test subject is classified as having a positive response.

Results

Clinical Database for Analysis

The database used for the analysis is available at https://iccvam.niehs.nih.gov/methods/immunotox/llna-panelDocs08.htm. The database includes information on 25 strong human sensitizers and 68 non-sensitizers. The database is organized by GHS potency category: 1A (strong) and 1B (other) sensitizers. The database includes information on the LLNA EC3 values for each sensitizer.

Figure 2. Comparison of LLNA and Human Data

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Figure 3. Comparison of LLNA and Human Data

Figure 4. Comparison of LLNA and Human Data

Table 2: Classification Rates for LLNA EC3 Prediction of Human Potency for 112 Substances

<table>
<thead>
<tr>
<th>Sensitizer Type</th>
<th>Classification Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong</td>
<td>77%</td>
</tr>
<tr>
<td>Other</td>
<td>75%</td>
</tr>
<tr>
<td>Nonsensitizers</td>
<td>88%</td>
</tr>
</tbody>
</table>

Summary

The LLNA EC3 classification rates for the 25 strong human sensitizers are shown in Table 2. The classification rates for strong sensitizers and other sensitizers are shown in Figure 5. The classification rates for nonsensitizers are shown in Figure 6. The optimum EC3 cutoff is 1.5% based on an overall correct classification rate of 62%.

Conclusions

The LLNA is a valid alternative to guinea pig test methods for many testing situations; however, it was not a valid alternative to sarcocyte test methods. Using the LLNA to categorize substances as strong sensitizers was proposed to be based on the LLNA EC3 value when LLNA EC3 > 2% as shown in Table 1. Following a rest period of several days, volunteers are again exposed to the test substance and observed for signs of irritation. If irritation is present, the test subject is classified as having a positive response.

Figures

Figure 1: A diagram showing the process of applying test substances. For each test subject, a patch is applied to their skin and left for a specified time. Following this, the patch is removed and the skin is observed for signs of irritation. If irritation is present, the test subject is classified as having a positive response.

Figure 2: A comparison of LLNA and human data for relative potency based on GHS potency categorization as shown in Figure 3.

Figure 3: A comparison of LLNA and human data for relative potency based on GHS potency categorization as shown in Figure 4.

Figure 4: A comparison of LLNA and human data for relative potency based on GHS potency categorization as shown in Figure 5.

Figure 5: A comparison of LLNA and human data for relative potency based on GHS potency categorization as shown in Figure 6.

Figure 6: A comparison of LLNA and human data for relative potency based on GHS potency categorization as shown in Figure 7.

Acknowledgments

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