Quantitative prediction of skin sensitisation potency based on structural alert spaces

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Overview

• Background

• Lhasa EC3 dataset
  • Data gathering and curation
  • Composition

• EC3 model
  • Methodology
  • Performance
  • Limitations
  • Demonstration

• Conclusions
Background: Derek Nexus and skin sensitisation

• Derek Nexus has 88 alerts for skin sensitisation
  • Based on assay data from mice, guinea pigs and human
• Currently we make qualitative predictions
  • Hazard identification
• We also want to be able to quantitatively estimate skin sensitisation potency
  • To aid in risk assessment
  • Desirable for ethical and regulatory reasons
  • Requires skin sensitisation potency data
Background: The LLNA

• The murine Local Lymph Node Assay (LLNA) is the gold standard assay for predicting skin sensitisation

• Measures the proliferation of T-lymphocytes in the lymph nodes
  • One of the key events in the skin sensitisation Adverse Outcome Pathway (AOP)

• Provides a measure of potency through an EC3 value
  • Estimated concentration of a compound that causes a 3-fold increase in lymphocyte proliferation compared with controls

Background: The LLNA

- EC3 values have been shown to correlate with human skin sensitisation potential
Background: The LLNA

- EC3 values have been shown to correlate with human skin sensitisation potential.
- Sensitisers can be assigned to one of four ECETOC potency categories:

<table>
<thead>
<tr>
<th>Extreme</th>
<th>Strong</th>
<th>Moderate</th>
<th>Weak</th>
</tr>
</thead>
<tbody>
<tr>
<td>EC3 (%)</td>
<td>0.1</td>
<td>1</td>
<td>10</td>
</tr>
</tbody>
</table>

Kimber et al., Food Chem. Toxicol. 2003, 41, 1799-1809
Lhasa EC3 dataset: Data gathering and curation

• We gathered as much publicly available EC3 data as possible

• The data was curated to ensure it was of high quality
  • Original experimental reports were located and examined
  • Unsuitable/unreliable data were not included in the final dataset

• When more than one LLNA study was found for the same compound the median EC3 value was taken
Lhasa EC3 dataset: Composition

• Data from 1051 LLNA studies were collected, resulting in a dataset containing 664 unique compounds

• Of these, 465 fire only one alert in Derek Nexus
  • These compounds span a good range of EC3 values
  • They include some non-sensitisers that fire a Derek alert
EC3 model: Initial considerations

- We would like to make use of existing knowledge captured in Derek’s alerts for skin sensitisation
  - Each alert space corresponds to a group of chemicals which are believed to react with skin proteins through the same mechanism
- Any model built needs to be transparent and interpretable
- The methodology must be scientifically defensible
**EC3 model: Possible methodologies**

- Regression models for different structural alerts
  - Some success, but not very interpretable

- Average EC3 values for each structural alert
  - Worked well for some alerts, but not others

- Finding nearest neighbours from within an alert space
  - Provided transparent and interpretable predictions
EC3 model: Possible methodologies

- Regression models for different structural alerts
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- Average EC3 values for each structural alert
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- Finding nearest neighbours from within an alert space
  - Provided transparent and interpretable predictions
EC3 model: Alert-based nearest neighbours

- **Query compound**
- **Lhasa EC3 dataset**

1. Match alert in Derek Nexus
2. Fingerprint query
3. Select NN
4. Fingerprint NN
   - ≥ 3 NN
   - < 3 NN: Insufficient data
5. Keep up to 10 most similar NN
6. Weighted mean $\frac{MW}{EC3}$
7. EC3 value predicted
EC3 model: **Alert-based nearest neighbours**

1. **Query compound**
   - Match alert in Derek Nexus
   - Fingerprint query

2. **Select NN**
   - Keep up to 10 most similar NN

3. **Weighted mean**
   - \( \frac{MW}{EC3} \)

4. **EC3 value predicted**

   - If \( \geq 3 \) NN
   - Insufficient data if \(< 3 \) NN
**EC3 model:** Alert-based nearest neighbours

1. **Query compound**
2. Match alert in Derek Nexus
3. Fingerprint query
4. Select NN
5. ≥ 3 NN: Fingerprint NN
6. < 3 NN: Insufficient data
7. Keep up to 10 most similar NN
8. Weighted mean $MW / EC3$
9. EC3 value predicted

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Chemical space
EC3 model: Alert-based nearest neighbours

Query compound → Match alert in Derek Nexus → Fingerprint query

Lhasa EC3 dataset → Select NN

≥ 3 NN → Fingerprint NN → Keep up to 10 most similar NN → Weighted mean \( MW / EC3 \) → EC3 value predicted

< 3 NN → Insufficient data

\[
\frac{MW_q}{EC3_q} = \frac{\sum_{n=1}^{N} \left( \frac{MW_n}{EC3_n} \right) T_{q,n}}{\sum_{n=1}^{N} T_{q,n}}
\]

- \( q \) = query compound
- \( N \) = number of nearest neighbours
- \( n \) = \( n^{th} \) nearest neighbour
- \( T_{q,n} \) = Tanimoto index between \( q \) and \( n \)

A. Natsch et al., *Toxicol. Sci.* 2015, 143, 319-332
EC3 model: Alert-based nearest neighbours

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- Lhasa EC3 dataset
- Insufficient data

Graph showing the relationship between similarity to query and EC3 value.
EC3 model: Performance

• The model was assessed using a validation set \((n = 46)\)

• Predictions were judged as accurate according to two separate criteria:
  • Within a factor of 3 of the experimental EC3 value
  • Within the same ECETOC potency category as the experimental EC3 value
EC3 model: Performance

When the model is wrong, it tends to over-predict rather than under-predict the potency.
EC3 model: Limitations

1. Coverage

- Directly linked to the size of the Lhasa EC3 dataset
  - This depends on the amount of publicly available LLNA data
- The EC3 model covers 39 of the skin sensitisation alerts within Derek Nexus
- Currently there are 49 alerts with fewer than three compounds in our dataset
  - Potential validation compounds: ~80% coverage
  - Do you have data you could share?
EC3 model: **Limitations**

2. Variability in LLNA data

- EC3 values can vary between different assay runs
  - This can be seen in the 87 compounds in the Lhasa EC3 dataset with multiple EC3 values

\[
\text{Fold variation} = \frac{EC3_{\text{max}}}{EC3_{\text{min}}}
\]

- Median = 2.3-fold variation

- This will affect the overall accuracy of the model
Conclusions

• We have developed an EC3 model which makes quantitative predictions of skin sensitisation potency
  • Built upon high quality, publicly available LLNA data
• Predictions are made by finding nearest neighbours to the query compound within defined structural alert spaces
  • Makes use of existing knowledge found in Derek Nexus alerts
• The model performs well against a validation set, both in terms of predicting EC3 values and potency categories
  • Provides transparent and interpretable predictions
Acknowledgements

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Thank you for your attention

Any questions?