Addressing the challenge of making negative predictions for skin sensitisation

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Introduction

• Why are negative predictions important?
  • Increasing reliance on *in silico* models as an alternative to *in vivo* testing
  • Incorrect negative predictions carry larger negative consequences
  • Therefore users need to have confidence in *in silico* negative predictions

• Can negative predictions be made for skin sensitisation?

<table>
<thead>
<tr>
<th>Opportunities</th>
<th>Challenges</th>
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</thead>
<tbody>
<tr>
<td>• Adverse outcome pathway with a single reactivity-driven molecular initiating event</td>
<td>• Prediction of an adverse outcome in humans using <em>in vivo</em> data from multiple assays and species</td>
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<tr>
<td>• Well-developed models for making positive <em>in silico</em> predictions (e.g. Derek Nexus contains 90 alerts for skin sensitisation)</td>
<td>• The quantity of <em>in vivo</em> data available in the public domain</td>
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</tbody>
</table>
Constructing the dataset

<table>
<thead>
<tr>
<th>Human</th>
<th>Standard animal</th>
<th>Non-standard animal</th>
<th>Other animal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basketter potency categories (1-6)</td>
<td>Guinea pig maximisation test Local Lymph Node Assay (LLNA)</td>
<td>Buehler test Epicutaneous tests Freund’s complete adjuvant test Optimisation tests Non-standard LLNA Single injection adjuvant test Split adjuvant test</td>
<td>Draize test Mouse ear swelling test</td>
</tr>
</tbody>
</table>

Data available:
- Human?
- Standard?
- Non-standard?
- Other?

Overall call:
- As human
- Conservative call within assay category
- Positive
- No call

- Human data: \( n = 414 \)
- Animal data: \( n = 3051 \)

Assign overall call

Negative prediction dataset: \( n = 2766 \)
Making negative predictions

These questions are answered by comparing the fragments in the query chemical to those of the chemicals in the negative prediction dataset.
Performance in 5-fold cross-validation

How often does each negative prediction outcome occur?

- Non-sensitiser: 79%
- Non-sens/Un: 12%
- Non-sens/Mis: 8%
- Non-sens/Mis+un: <1%

How often is each negative prediction outcome correct?

prevalence of non-sensitisers = 51%

- Non-alerting: 74%
- Non-sensitiser: 77%
- Non-sens/Un: 66%
- Non-sens/Mis: 52%
Expert review: Case study 1

• Longifolene may act as a prehapten, probably by producing a sensitising allylic hydroperoxide.

• As africanol lacks an allyl group, confidence in the negative prediction is likely to increase.

Africanol (natural product)

NON-SENSITISER with misclassified features

Longifolene (34% similar)
Human positive (weak)
LLNA positive (moderate)
Possible prehapten
Expert review: Case study 2

- The two chemicals are highly structurally similar, and share the same overall scaffold.
- Given the high similarity to the false negative, confidence in the negative prediction is likely to decrease.

Fenpyrithrin (63% similar)
Guinea pig split adjuvant test positive (5/5 animals sensitised)

Cyhalothrin (insecticide)

NON-SENSITISER with misclassified features
Conclusions

- Reliable negative predictions of human skin sensitisation can be made
  - The method uses an *in silico* fragmentation approach
  - The majority of non-alerting chemicals in the cross-validation were simply predicted to be **non-sensitisers**, the outcome that can be treated with the most confidence
- Features which increase uncertainty are highlighted for expert review
  - These are known as **misclassified** or **unclassified** features
  - Expert review may be able to resolve some of this residual uncertainty
- This work, together with the results of an external validation using proprietary data shared by our members, has recently been accepted for publication
Acknowledgements

• Donna Macmillan

• Rich Williams

• Many other colleagues at Lhasa Limited

• All of our members who have recently shared skin sensitisation data with us
Thank you for your attention

Are there any questions?