Assessing whether expert knowledge and statistical *in silico* models can be used to predict the sensitisation potential of extractables and leachables

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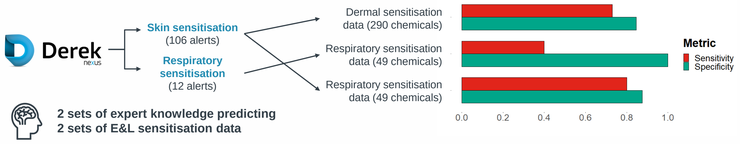
1. E&Ls need to be assessed for sensitisation

- Extractables and leachables (E&L) can be present in pharmaceutical products and medical devices and need to undergo a toxicological risk assessment.
- Sensitisation is one endpoint of concern,[1] alongside mutagenicity and systemic toxicity. E&Ls often lack sensitisation data and new data can be hard to generate.
- This study sought to investigate the role that *in silico* sensitisation models could play in predicting the sensitisation hazard and potency of E&Ls.

1. Parris et al., *Crit. Rev. Toxicol.*, **2022**, *52*, 125-138; Parris et al., *PDA J. Pharm. Sci. Technol.*, **2023**, manuscript submitted

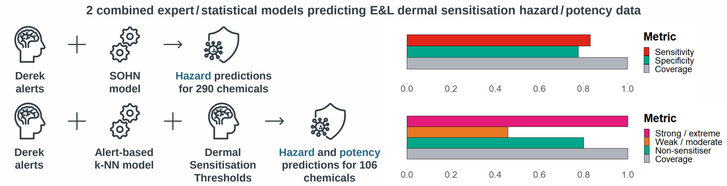
3. Expert knowledge can predict sensitisation



- Derek Nexus[10] contains an extensive set of structural alerts for the skin sensitisation endpoint, and a less-well developed set for respiratory sensitisation.
- The skin sensitisation alerts accurately predicted the dermal sensitisation potential of E&Ls (sensitivity = 73%), but the respiratory sensitisation alerts did not fire for many E&Ls which were experimental positives (sensitivity = 40%). However, the skin sensitisation alerts did predict well for respiratory sensitisers (sensitivity = 80%).[9]

10. Derek Nexus v6.2.1, Lhasa Limited, **2022**

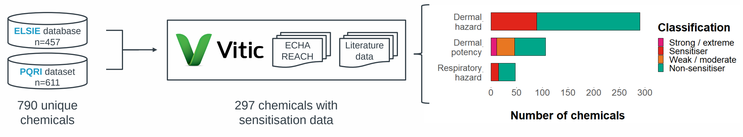
5. Combining approaches improves predictions



- Combining Derek's alerts with the best SOHN in a conservative fashion improved the sensitivity (83%) at the cost of specificity (78%), compared to the individual models.
- Derek was also combined with an existing alert-based k-NN model[11] and the Dermal Sensitisation Thresholds[12] to accurately predict strong / extreme sensitisers (100%).
- Comprehensive coverage was possible as expert predictions are always provided.

11. Canipa et al, *J. Appl. Toxicol.*, **2017**, *37*, 985-995
12. Chilton et al, *Regul. Toxicol. Pharmacol.*, **2022**, *133*, 105200

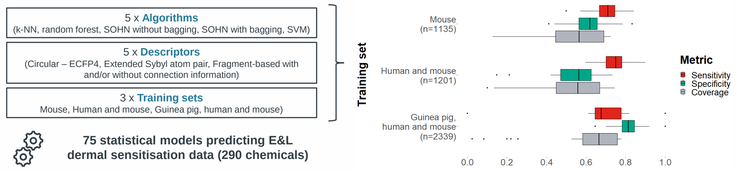
2. A large E&L dataset has been collated



- Structures in ELSIE's E&L database were downloaded from the relevant list stored on the US EPA's CompTox dashboard.[2]
- Structures in PQRI's E&L dataset[3] were generated from names and CAS numbers using Vitic,[4] ChemIDplus / PubChem,[5] and the Chemical Identifier Resolver.[6]
- Sensitisation data was retrieved from Vitic, REACH dossiers[7] and the literature.[8,9]

2. https://comptox.epa.gov/dashboard/chemical-lists/ELSIE
3. https://pqri.org/wp-content/uploads/2022/03/PQRI-PDP-Recommendation-2022.pdf
4. Vitic v4.1.0, Lhasa Limited, **2021**
5. https://pubchem.ncbi.nlm.nih.gov/
6. https://cactus.nci.nih.gov/chemical/structure
7. http://echa.europa.eu/
8. Api et al, *Dermatitis*, **2017**, *28*, 299-307; Basketter et al, *Dermatitis*, **2014**, *25*, 11-21
9. Golden et al, *Chem. Res. Toxicol.*, **2021**, *34*, 473-482

4. Statistical sensitisation models can be built



- 75 models were built using various algorithms, descriptors and training sets.
- Sensitivity remained similar across the three training sets, but the models built on the largest training set (n=2339) tended to have a higher coverage and specificity.
- The best performing model with a minimum coverage of 70% was a SOHN (without bagging) built using an ECFP4 circular fingerprint (sensitivity = 71%, specificity = 82%, coverage = 73%). This model was taken forwards for further experimentation.

6. *In silico* models can help assess risk of E&Ls

- An extensive E&L dataset has been created and any publicly available *in vivo* sensitisation data for these chemicals has been gathered.
- Expert knowledge, in the form of structural alerts in Derek Nexus, can accurately predict the dermal and respiratory sensitisation potential of E&Ls.
- Statistical models can be built to predict the dermal sensitisation potential of E&Ls, with a similar performance to well-established expert knowledge.
- Combining expert knowledge and a statistical model leads to an approach with improved sensitivity and high coverage for predicting dermal sensitisation hazard.
- Expert knowledge can also be combined with an alert-based k-NN model and the Dermal Sensitisation Thresholds to conservatively predict sensitisation potency.
- Both expert knowledge-based and statistical *in silico* models can be used to assess the sensitisation potential of E&Ls as part of a wider toxicological risk assessment.