Assessment of the dermal sensitisation potency of extractables and leachables using existing data and *in silico* methods

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Introduction

There is a recognised need to assess the sensitisation potential of extractable and leachable (E&L) compounds as part of the safety assessment of impurities, alongside other toxicological endpoints of concern. This is typically approached by applying a safety threshold, such as the 5 µg / day threshold for sensitisers / irritants recommended by the PQRI (**Figure 1**).[1]

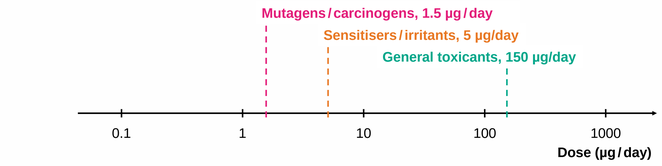

Figure 1. Commonly used thresholds in E&L safety assessment.

However, the potency of known skin sensitisers spans several orders of magnitude.[2] While threshold approaches are likely to be protective, they may lead to the excessive control of weak / moderate sensitisers which pose very little risk in an E&L exposure scenario. This study sought to investigate the role that *in silico* models, including expert systems and machine learning algorithms, could play in predicting dermal sensitisation potency, with the aim of identifying strong / extreme sensitisers to inform a wider E&L sensitisation safety assessment.

Dataset

Dermal and respiratory sensitisation data was collected from the public literature for a total of 231 E&L compounds (**Figure 2**), taken from the ELSIE database.[3] 229 chemicals had dermal hazard data in humans, mice and / or guinea pigs, 54 had dermal potency data in mice, and 37 had respiratory hazard data in humans (**Figure 3**).

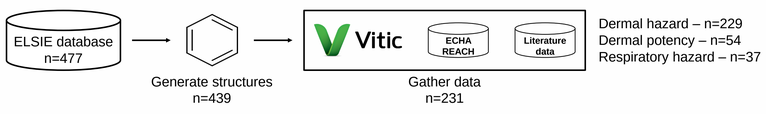

Figure 2. Data collection workflow.

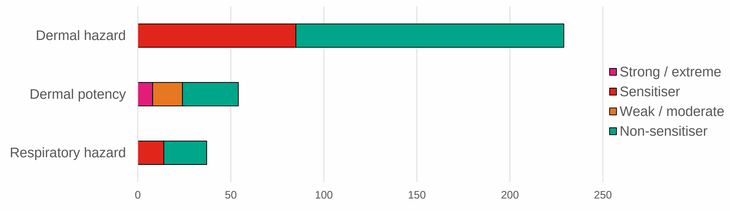

Figure 3. Distribution of publicly available sensitisation data for E&Ls.

Models

Different *in silico* models and combinations thereof were used to predict the dermal / respiratory sensitisation hazard and potency of the E&L chemicals (**Table 1**). These models were based on expert knowledge (structural alerts in Derek Nexus[4]), machine learning algorithms (Self-Organising Hypothesis Network (SOHN)[5] and k-nearest neighbours (k-NN)[6]) and / or existing data (Dermal Sensitisation Thresholds (DSTs)[7]). The performance of these models is shown in **Table 2** and **Table 3**.

***In silico* model(s)**	**Methodology**	**Endpoint**	**Prediction**
Derek	Expert knowledge	Dermal and respiratory sensitisation	Hazard
SOHN	Machine learning	Dermal sensitisation	Hazard
Derek + SOHN	Expert knowledge and machine learning	Dermal sensitisation	Hazard
Derek + k-NN	Expert knowledge and machine learning	Dermal sensitisation	Hazard and potency
Derek + k-NN + DSTs	Expert knowledge, machine learning and existing data	Dermal sensitisation	Hazard and potency

Table 1. Description of the various *in silico* models used in this study.

***In silico* model(s)**	**Endpoint**	**Balanced accuracy (%)**	**Sensitivity (%)**	**Specificity (%)**
Derek skin sensitisation alerts	Dermal sensitisation	72	60	83
Derek respiratory sensitisation alerts	Respiratory sensitisation	68	36	100
Derek skin sensitisation alerts	Respiratory sensitisation	81	79	83
SOHN	Dermal sensitisation	60	54	65
Derek + SOHN	Dermal sensitisation	67	75	58

Table 2. Performance in predicting E&L sensitisation hazard using human/animal data.

***In silico* model(s)**	**Endpoint**	**Strong / extreme (%)**	**Non-sensitising / weak / moderate (%)**	**Prediction available (%)**
Derek + k-NN	Dermal sensitisation	83	91	91
Derek + k-NN + DSTs	Dermal sensitisation	88	78	100

Table 3. Performance in predicting E&L dermal sensitisation potency using murine data.

Workflow

The best performing modelling approach of those tested (Derek + k-NN + DSTs) employs the following workflow (**Figure 4**):

① E&L chemicals are classified as non-reactive, reactive or High Potency Category (HPC) using the alerts found in Derek Nexus.

② Non-reactive chemicals are predicted to be non-sensitising / weak / moderate based on the non-reactive DST.

③ The potency of reactive chemicals is binned into its appropriate category using predictions from Derek's k-NN model.

④ If an EC3 prediction is not available, the chemical is predicted to be strong / extreme based on the reactive DST.

⑤ HPC chemicals are predicted to be strong / extreme based on the HPC DST.

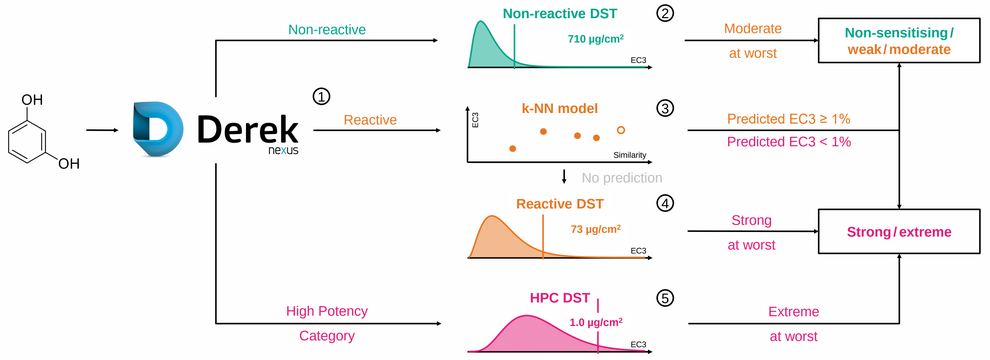

Figure 4. Workflow for classifying E&L as strong / extreme sensitisers using Derek + k-NN + DSTs.

Conclusions

- Expert knowledge can predict the dermal and respiratory sensitisation of E&L, but a purely machine learnt approach struggles in this chemical space.
- Combining an expert system with a machine learnt SOHN model does not add value.
- Combining Derek's skin sensitisation alerts, k-NN EC3 model, and the established Dermal Sensitisation Thresholds can conservatively identify E&L which are strong / extreme sensitisers.
- This proposed workflow could be used for E&L sensitisation safety assessment under ICH Q3E.

References

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