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

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# Agenda

- Introduction
- *In silico* tools for predicting sensitisation
  - Expert knowledge
  - Machine learning
- Sensitisation data for E&L
  - Dermal (hazard and potency)
  - Respiratory
- Predicting the sensitisation potential of E&L
  - Models (expert knowledge and machine learning)
  - Proposed workflow
- Conclusions

# Introduction to Lhasa Limited

- Established in 1983
- HQ located in Leeds, United Kingdom
- Not-for-profit & Educational Charity
- Facilitate collaborative data sharing projects in the chemistry-related industries
- Controlled by our members
- Creators of knowledge base, statistical and database systems

Derek nexus · Zeneth · Meteor nexus · Setaria · Sarah nexus · Mirabilis · Vitic

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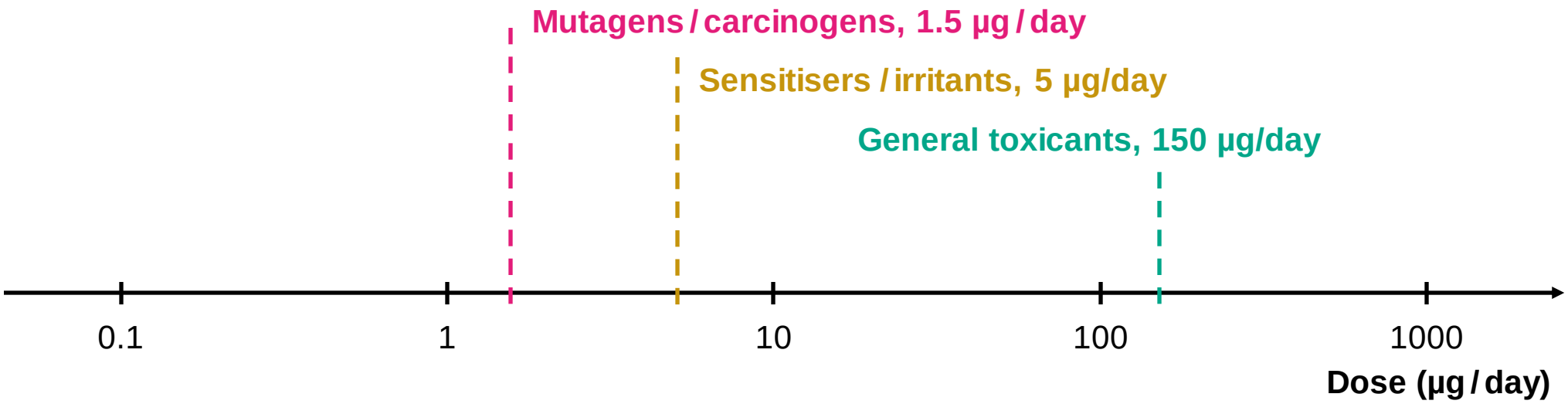
# Introduction

- There is a recognised need to assess the sensitisation potential of E&L
  - Typically approached by applying a safety threshold, such as those proposed by PQRI[1]




- However, dermal sensitisation potency is known to span 5 orders of magnitude
  - Thresholds may lead to excessive control of weak / moderate sensitisers
  - Can *in silico* models help identify strong / extreme sensitisers?

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1. Ball et al., *Toxicol. Sci.* **2007**, *97*, 226-236; Broschard et al, *Regul. Toxicol. Pharmacol.* **2016**, *81*, 201-211

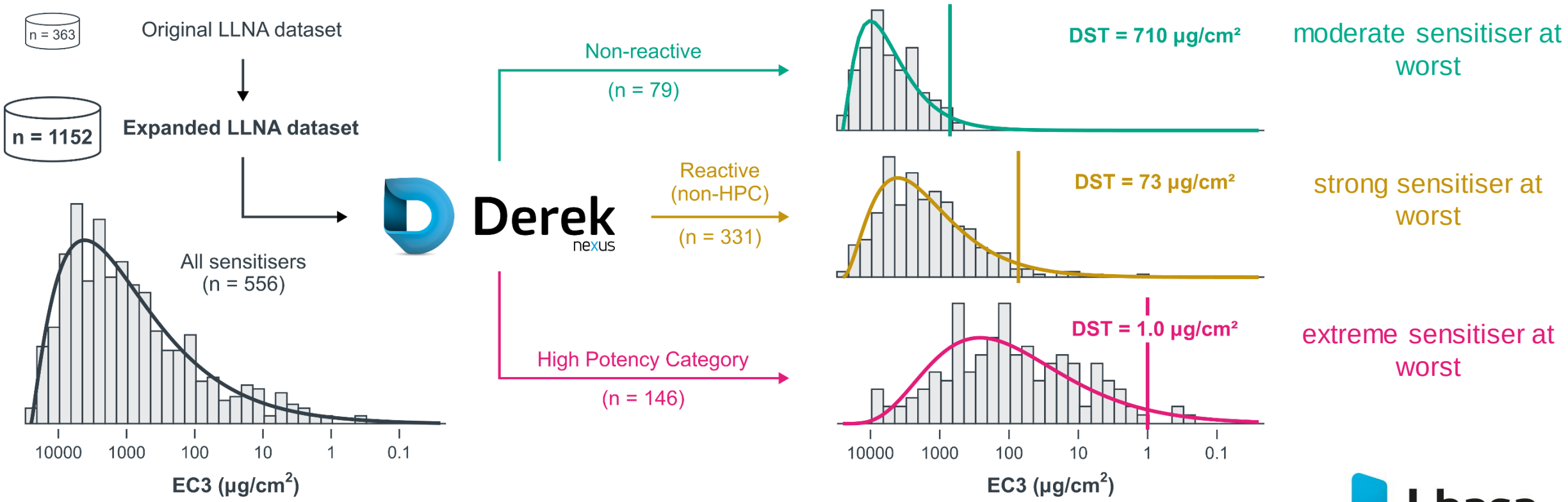
# *In silico* tools for predicting sensitisation

- Expert knowledge
  - Derek's skin sensitisation alerts
    - Predict binary sensitisation hazard
    - 100 alerts in the knowledge base
    - Explicit negative predictions available[1]
  - Derek's respiratory sensitisation alerts
    - Predict binary sensitisation hazard
    - 12 alerts in the knowledge base
  - High Potency Category (HPC) alerts[2]
    - Identify reactive features likely to be associated with high potency (extreme sensitisers)
    - Published in the context of the Dermal Sensitisation Threshold
    - Recently have been updated and encoded into Derek[3]


1. Chilton et al., *Regul. Toxicol. Pharmacol.* **2018**, *95*, 227-235
2. Roberts et al., *Regul. Toxicol. Pharmacol.* **2015**, *72*, 683-693
3. Chilton et al., *Regul. Toxicol. Pharmacol.* **2022**, manuscript submitted

# *In silico* tools for predicting sensitisation

- Expert knowledge
  - Dermal Sensitisation Thresholds[1,2]





1. Safford et al., *Regul. Toxicol. Pharmacol.* **2015**, *72*, 694-701
2. Chilton et al., *Regul. Toxicol. Pharmacol.* **2022**, manuscript submitted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# *In silico* tools for predicting sensitisation

- Machine learning
  - Self Organising Hypothesis Network (SOHN)[1]
    - Well-established model for predicting *in vitro* mutagenicity
    - Could this approach be used to predict binary sensitisation hazard?
      - Similar reactivity-based mechanism of toxicity
      - Reasonable amount of data in the public domain
  - Derek's EC3 model[2]
    - Predicts EC3 values for chemicals firing a skin sensitisation alert
    - Uses an alert-based k-NN model to perform automated, mechanistic read-across


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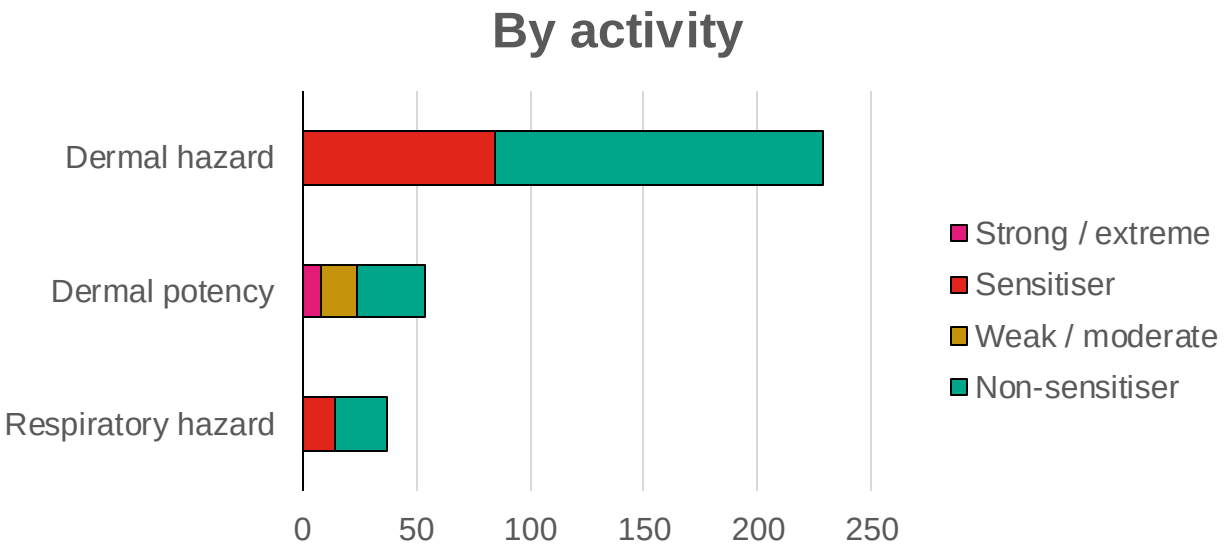
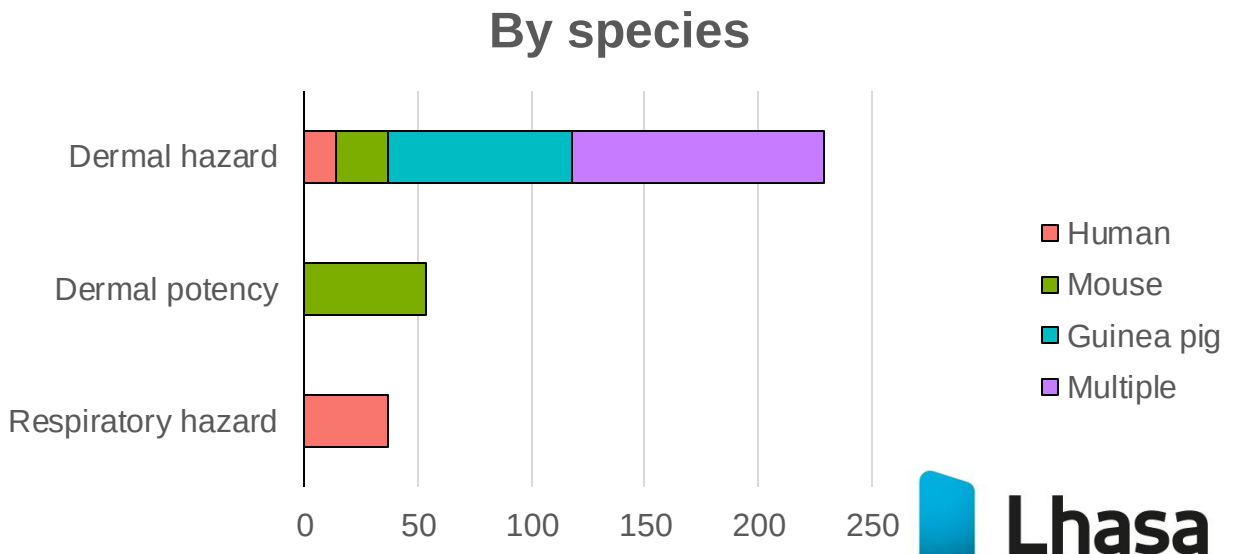
1. Hanser et al., *J. Cheminform.* **2014**, *6*, 21
2. Canipa et al., *J. App. Toxicol.* **2017**, *8*, 985-995

# Sensitisation data for E&L

- What sensitisation data is available for E&L?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# Expert knowledge

- Derek alerts
  - How well does Derek predict dermal sensitisation?

| Test set | Endpoint | Sensitivity (%) | Specificity (%) |
|---|---|---|---|
| Public dataset (n=3141) | Skin sensitisation | 79 | 64 |
| E&L dermal sensitisation dataset (n=229) | | 60 | 83 |

  - How well does Derek predict respiratory sensitisation?

| Test set | Endpoint | Sensitivity (%) | Specificity (%) |
|---|---|---|---|
| Public dataset (n=247) | Respiratory sensitisation | 36 | 100 |
| | Skin sensitisation | 80 | 67 |
| E&L respiratory sensitisation dataset (n=37) | Respiratory sensitisation | 36 | 100 |
| | Skin sensitisation | 79 | 83 |

    - Skin sensitisation alerts cover known respiratory sensitisers well[1]

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1. Golden et al., *Chem. Res. Toxicol.* **2021**, *34*, 473-482

# Machine learning

- SOHN model
  - How well does a machine learnt model predict dermal sensitisation?

| Training set data | Training set size | Test set | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|
| Mouse (LLNA) | 1236 | 5-fold cross-validation | 66 | 76 |
| | | E&L dermal sensitisation dataset (n=229) | 54 | 65 |
| Human + mouse | 1308 | 5-fold cross-validation | 61 | 76 |
| | | E&L dermal sensitisation dataset (n=229) | 48 | 69 |
| Human + mouse + guinea pig | 3141 | 5-fold cross-validation | 59 | 72 |
| | | E&L dermal sensitisation dataset (n=229) | 39 | 85 |

- Including more assays increases training set size but decreases model performance
- Models struggle to predict well within E&L chemical space

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# Expert knowledge + machine learning

- Derek alerts + SOHN model
  - Does combining two systems add value?

| Test set | Model(s) | Sensitivity (%) | Specificity (%) |
|---|---|---|---|
| E&L dermal sensitisation dataset (n=229) | Derek (skin sensitisation alerts) | 60 | 83 |
| | SOHN (trained on LLNA data) | 54 | 65 |
| | Derek + SOHN (conservative) | 75 | 58 |

    - Adding a SOHN model does improve the sensitivity
  - When the systems disagree, who is right?

| Test set | Model(s) | Sensitivity (%) | Specificity (%) |
|---|---|---|---|
| Subset of E&L dermal sensitisation dataset where Derek and SOHN disagree (n=77) | Derek | 58 | 78 |
| | SOHN | 42 | 22 |

    - Derek is correct 70% of the time when the two systems disagree

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# Expert knowledge + machine learning

- Derek alerts + k-NN model


- How well does a tiered approach predict potency?

| Test set | Strong / extreme (%) | Non-sensitising / weak / moderate (%) | Prediction available (%) |
|---|---|---|---|
| E&L dermal potency sensitisation dataset (n=54) | 83 | 91 | 91 |

- Accurate identification of strong / extreme sensitisers
- However, predictions are not always available
- Could the DSTs be used as additional worst-case scenario predictions?

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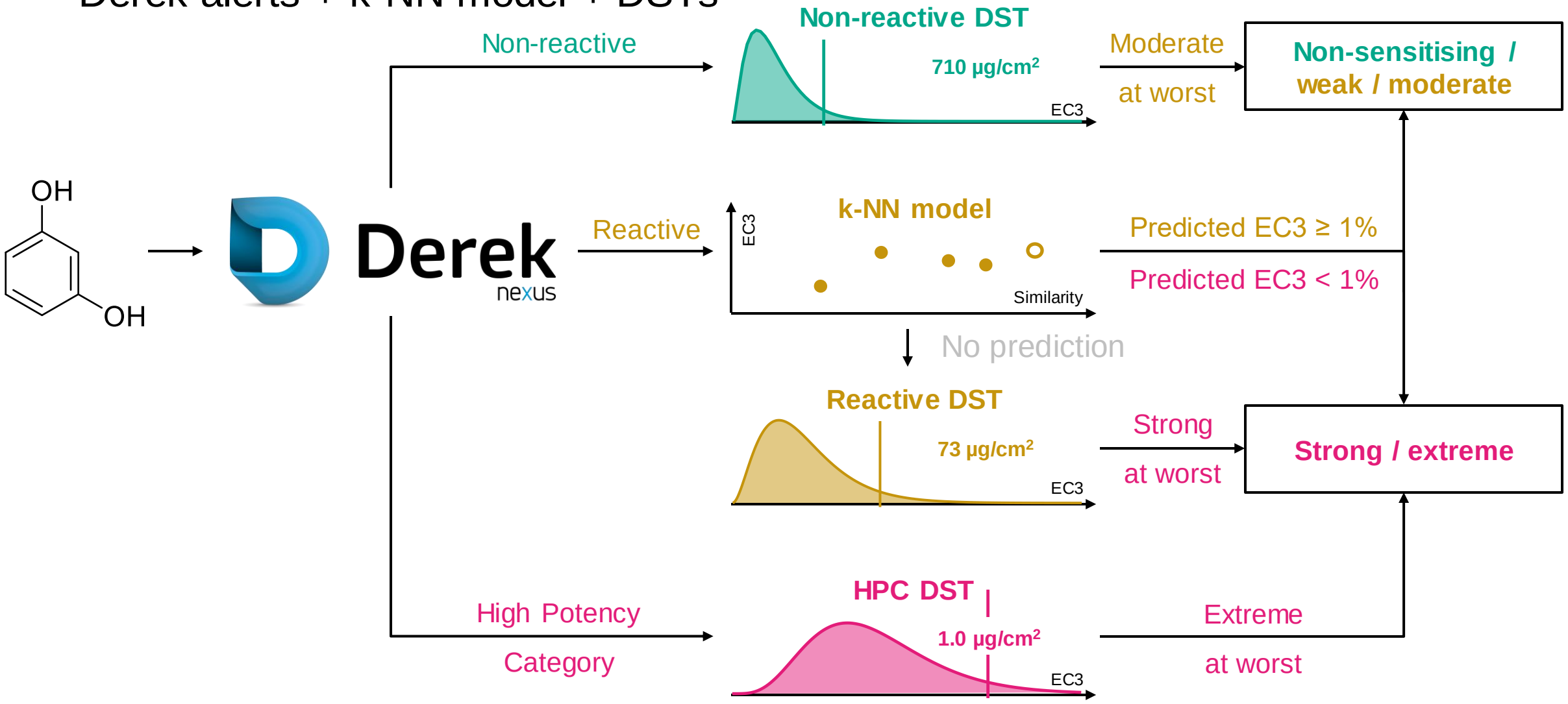
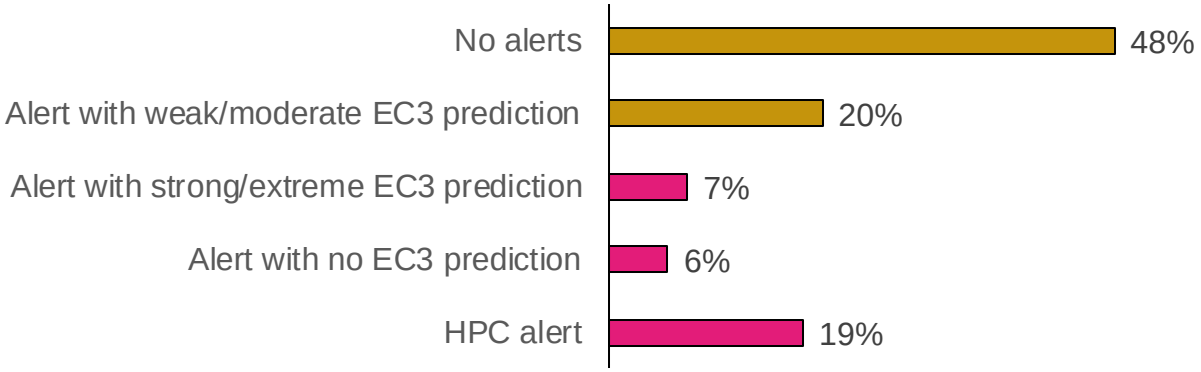
# Proposed workflow

- Derek alerts + k-NN model + DSTs

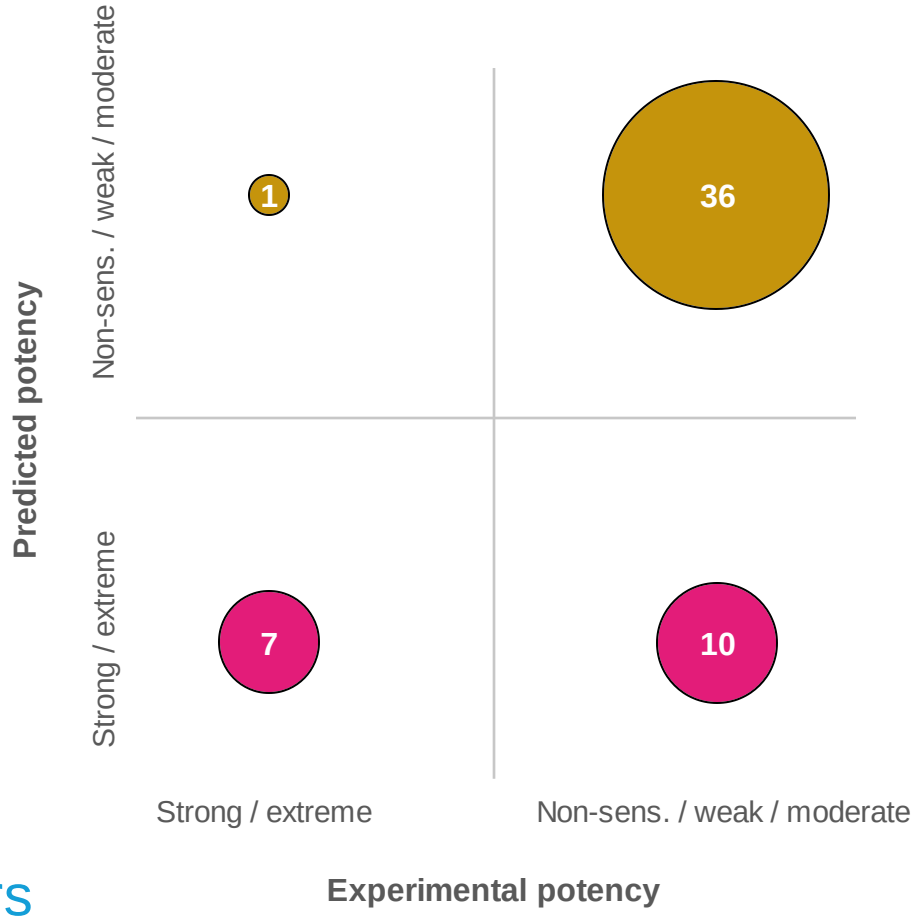


# Proposed workflow

- Derek alerts + k-NN model + DSTs




| Test set | Strong / extreme (%) | Non-sensitising / weak / moderate (%) | Prediction available (%) |
|---|---|---|---|
| E&L dermal potency sensitisation dataset (n=54) | 88 | 78 | 100 |




- Accurate identification of strong / extreme sensitisers
- Predictions are conservative
- Predictions are always available

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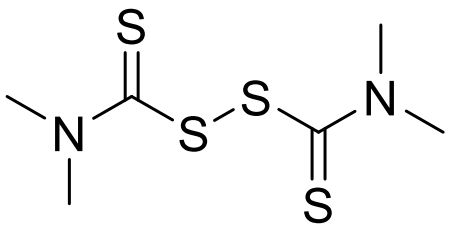
# Proposed workflow

- Derek alerts + k-NN model + DSTs
  - Is there a risk of missing strong / extreme sensitisers using this approach?
- Tetramethylthiuram disulfide (137-26-8)




  - Reactive, predicted EC3 = 2.5% (moderate)
  - Median experimental EC3 = 0.70% (strong)
    - **5.2%** - standard LLNA protocol, good dose-response observed, negative at 2.5% and 5% (Gerberick et al, Dermatitis 2005, 16, 157-202)
    - **0.70%** - modified LLNA with 1% SLS pre-application to increase assay sensitivity (De Jong et al, Toxicol. Sci. 2002, 66, 226-232)
    - **0.66%** - modified LLNA with 1% SLS pre-application to increase assay sensitivity (Van Och et al, Toxicology 2000, 146, 49-59)
  - Experimental potency likely to be over-estimated

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# Conclusions

- The sensitisation potential of E&L can be assessed using *in silico* methods
  - Expert knowledge can predict the dermal and respiratory sensitisation of E&L
  - However, a purely machine learnt approach struggles in this chemical space
- Combining expert knowledge with machine learning can improve performance
  - Derek alerts + SOHN model improves sensitivity, but 2nd system does not add value
  - Derek alerts + k-NN model performs well, but cannot always provide a prediction
- A novel E&L sensitisation workflow has been proposed
  - Uses Derek alerts + k-NN model + Dermal Sensitisation Thresholds
  - Can conservatively identify E&L which are strong / extreme sensitisers
  - These predictions could be used to inform further E&L safety assessment

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# Acknowledgements


- Lhasa Limited
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  - Sensitisation sub-stream

# Thanks for listening

Any questions?

shared **knowledge** • shared **progress**

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