Negative Predictions for Skin Sensitisation

46th ICGM, 16th March 2017

Baltimore, Maryland

Martyn Chilton

Scientist

Martyn.Chilton@lhasalimited.org

Overview

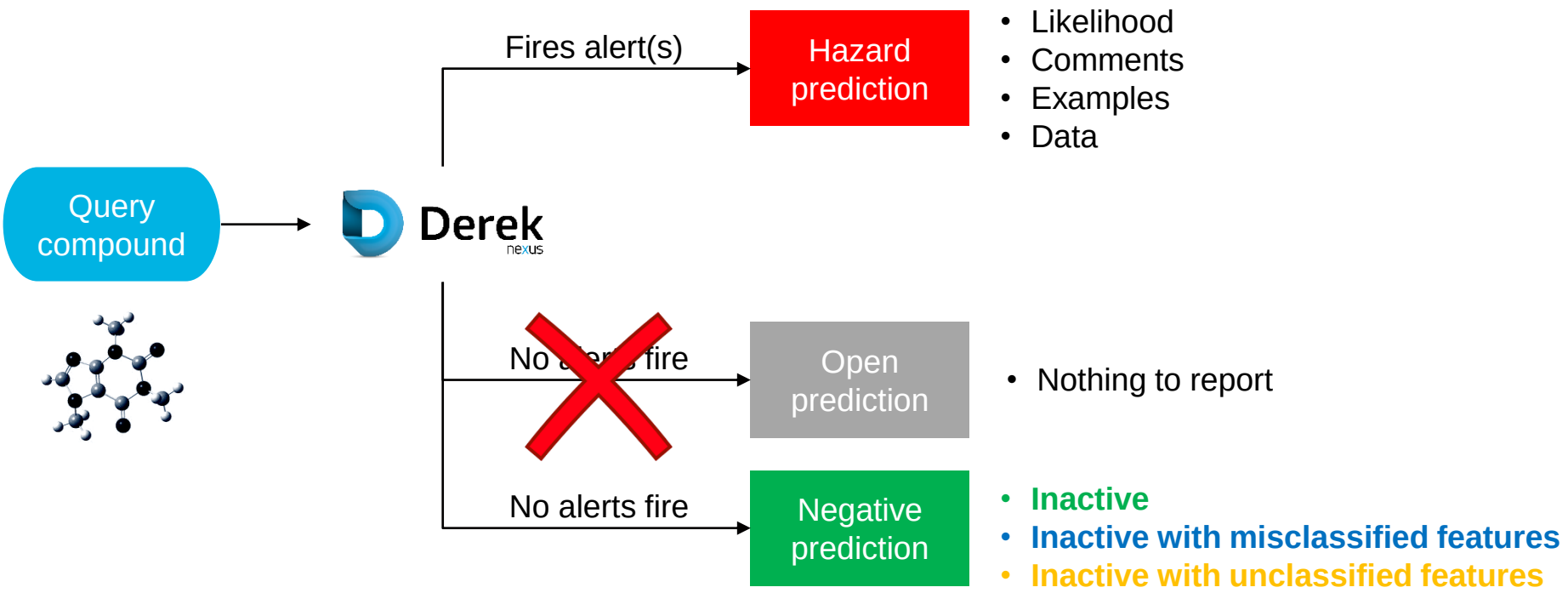
- Background
  - Making negative predictions for mutagenicity *in vitro*
  - Specific challenges around making negative predictions for skin sensitisation
- Results
  - Constructing a skin sensitisation reference dataset
  - Performance of the model
  - The importance of expert review
- Conclusions

Background

- Negative Predictions are important…
  - *In silico* models are expected to be relied upon increasingly as an alternative to *in vivo* testing
  - Model users and regulators will need to have confidence in negative *in silico* predictions if they are to be used to show that chemicals are safe for humans and the environment

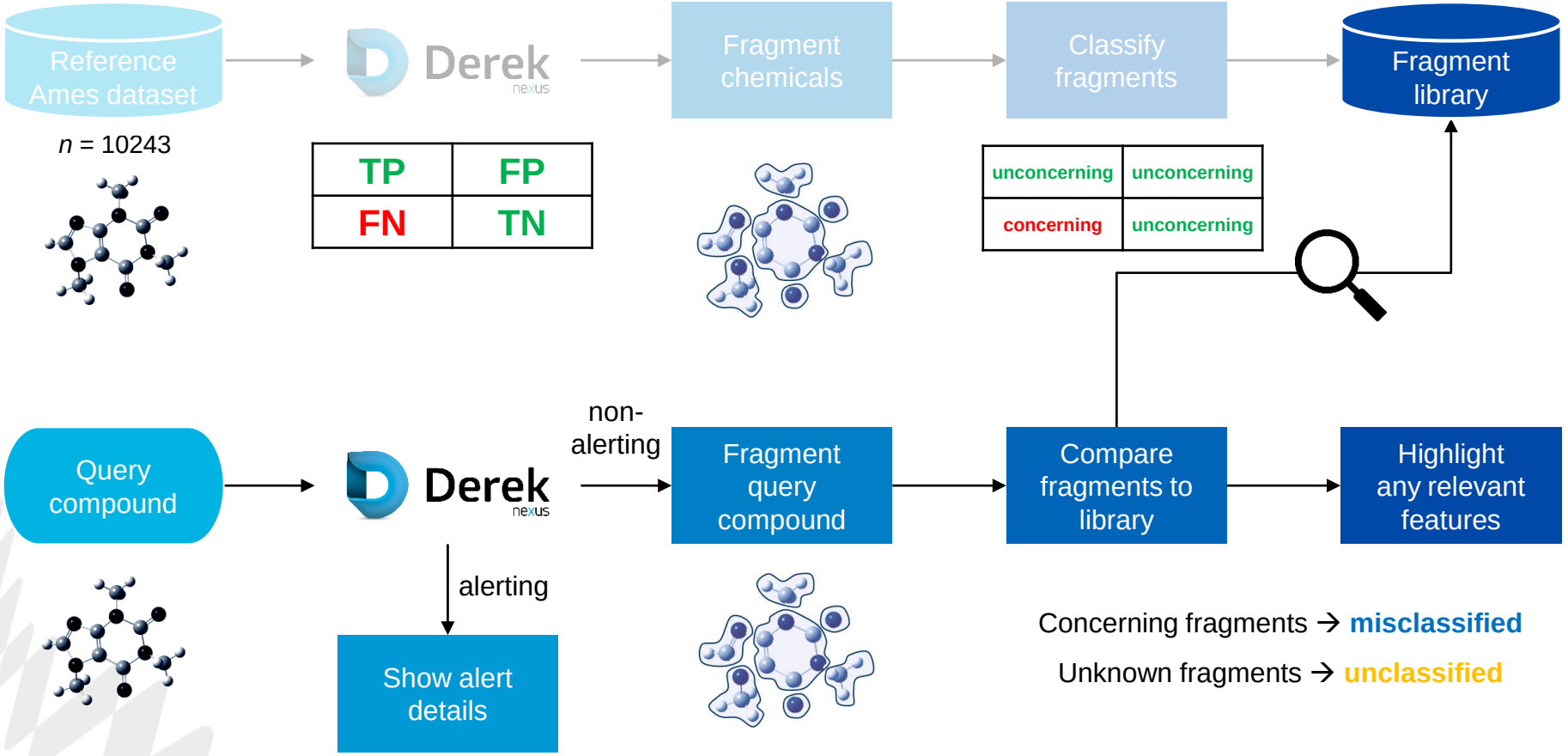
- … but difficult
  - Models typically try to discern the features of a chemical that are thought to be responsible for a particular toxicity
  - Therefore is the lack of a positive prediction for toxicity sufficient evidence to make a negative prediction?

Mutagenicity *in vitro*

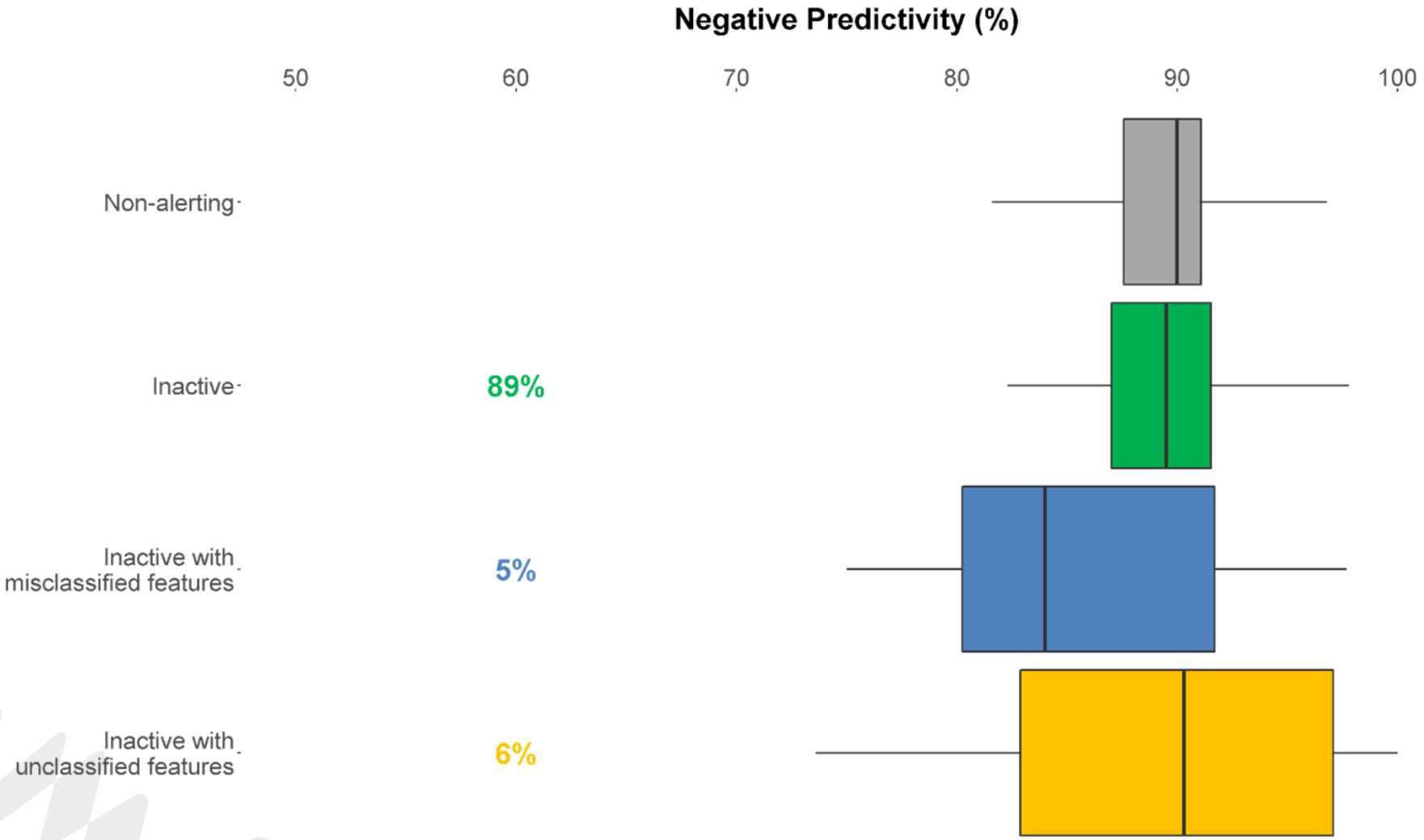


- Reactivity-based mechanism (DNA adduct formation)
- Fragments can capture reactivity well
- Sufficiently large dataset

Methodology in Derek Nexus



Performance for mutagenicity *in vitro*



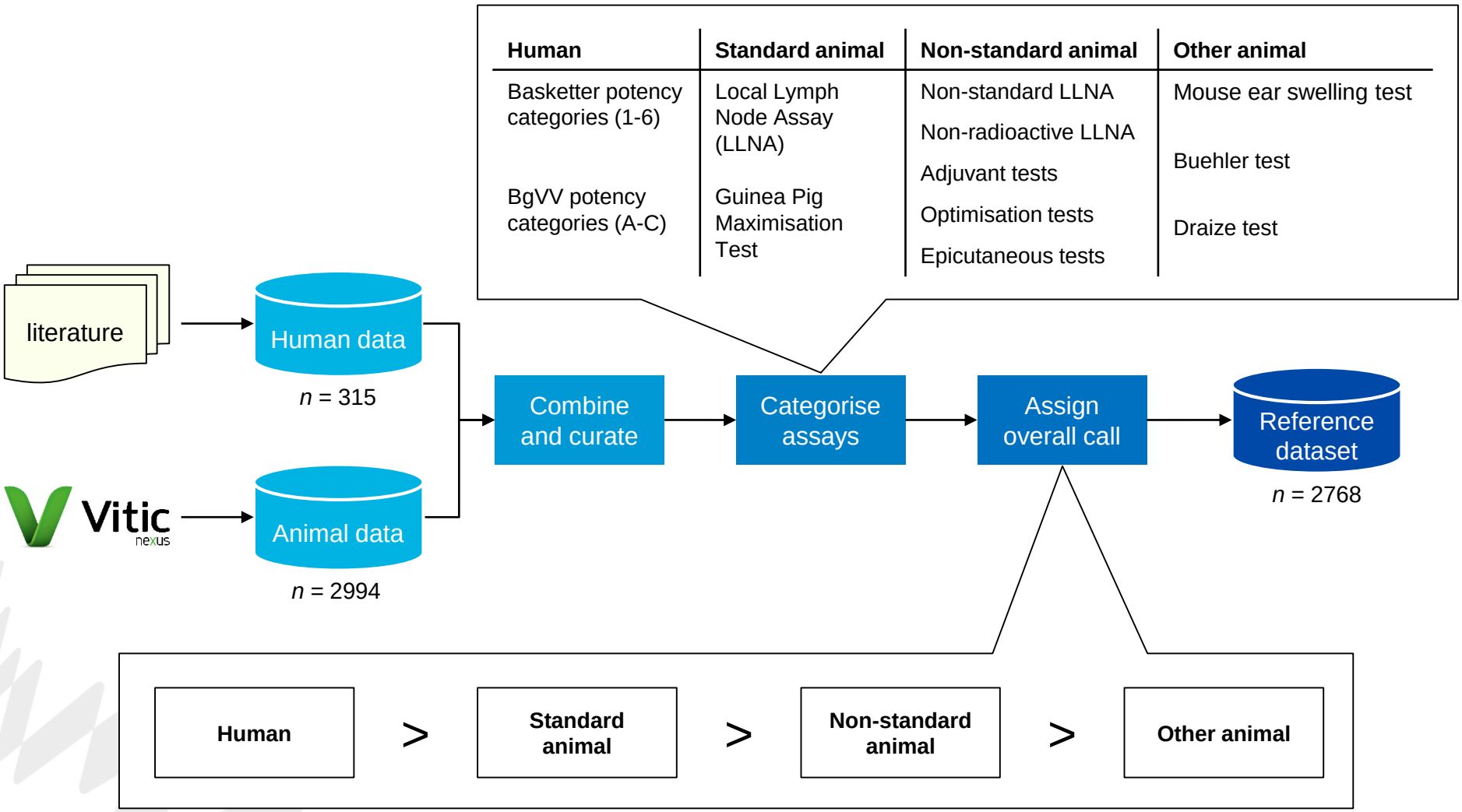
R. Williams *et al., Regul. Toxicol. Pharmacol.* **2016**, *76*, 79-86

Comparing skin sensitisation to mutagenicity

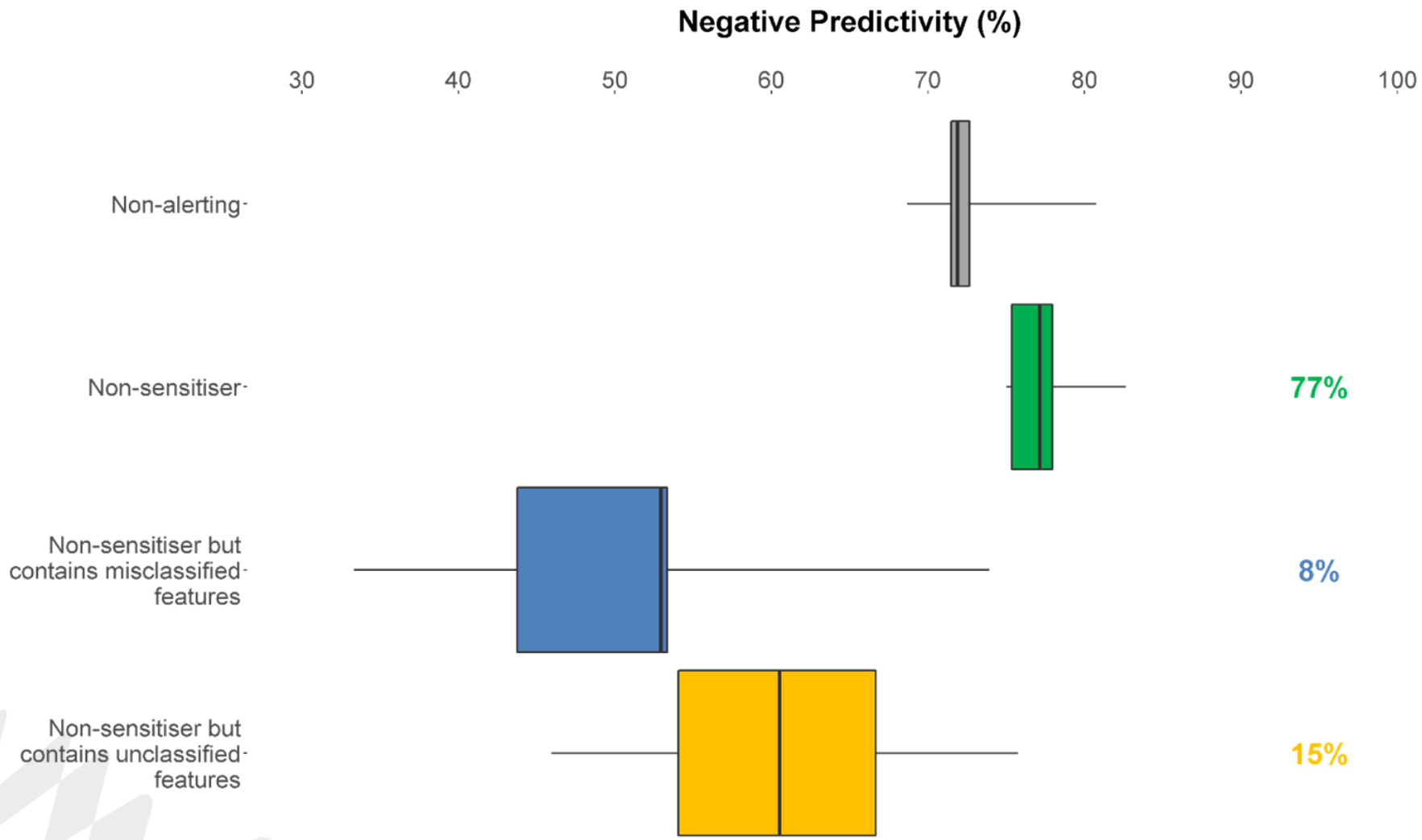
- Similarities
  - Also reactivity driven (protein adduct formation)
  - Good coverage of the endpoint (87 alerts)

- Challenges
  - Multiple species/assays
  - Predicting an *in vivo* adverse outcome rather than the result of an *in vitro* assay
  - Amount of data available

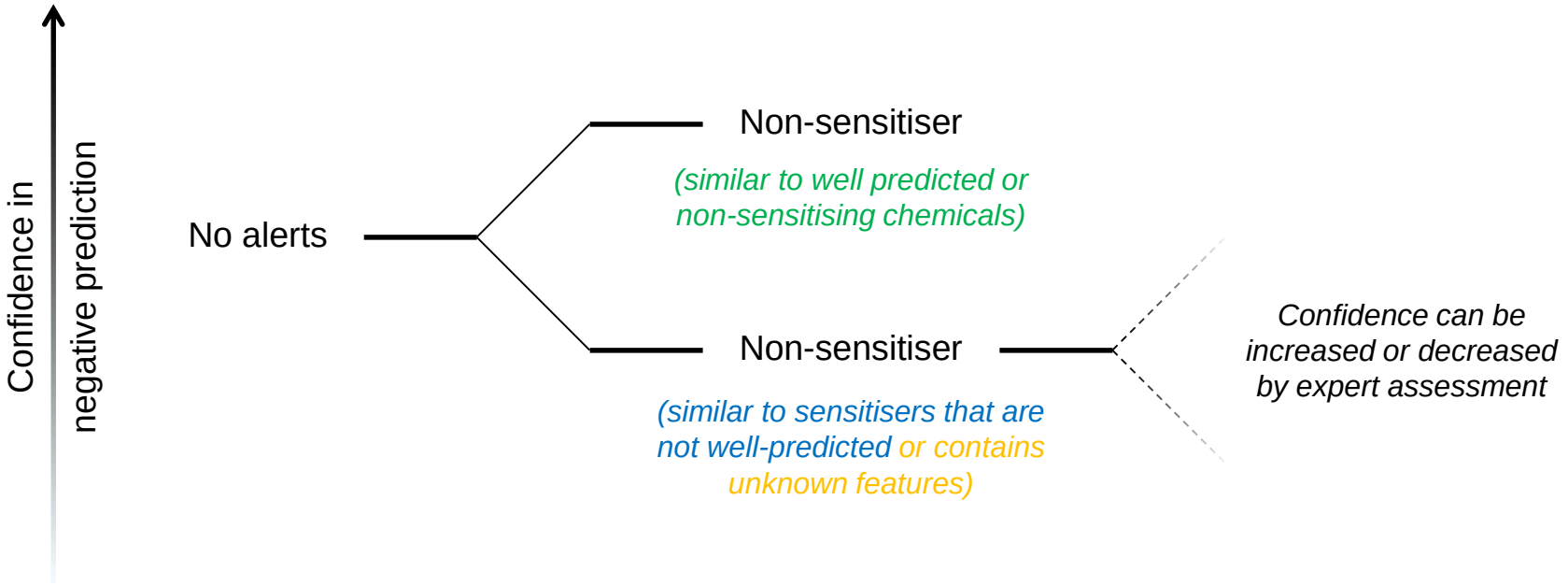
Constructing the reference dataset



Performance for skin sensitisation



The importance of expert review



- **Misclassified feature:** many compounds in the reference dataset contain the same feature and are similar to the query chemical

- **Unclassified feature:** many known non-sensitisers contain the same feature as the query chemical

Conclusions

- Demonstrated that the negative predictions methodology can be extended to skin sensitisation
  - This functionality will be included in the next Derek Nexus release
- Planning to validate the approach using member data
  - Aiming to produce a joint publication with the validation results
  - Let us know if you are interested in being involved in this by sharing skin sensitisation data (guinea pig, mouse or human)

Acknowledgements

- Donna Macmillan
- Rich Williams
- Susanne Stalford

Thank you for your attention

Any questions?

Lhasa Limited Registered Office
Granary Wharf House, 2 Canal Wharf, Leeds LS11 5PS
Registered Charity (290866)

+44 (0)113 394 6020
info@lhasalimited.org
www.lhasalimited.org