

Updated Dermal Sensitisation Thresholds derived using an *in silico* expert system and an expanded Local Lymph Node Assay dataset

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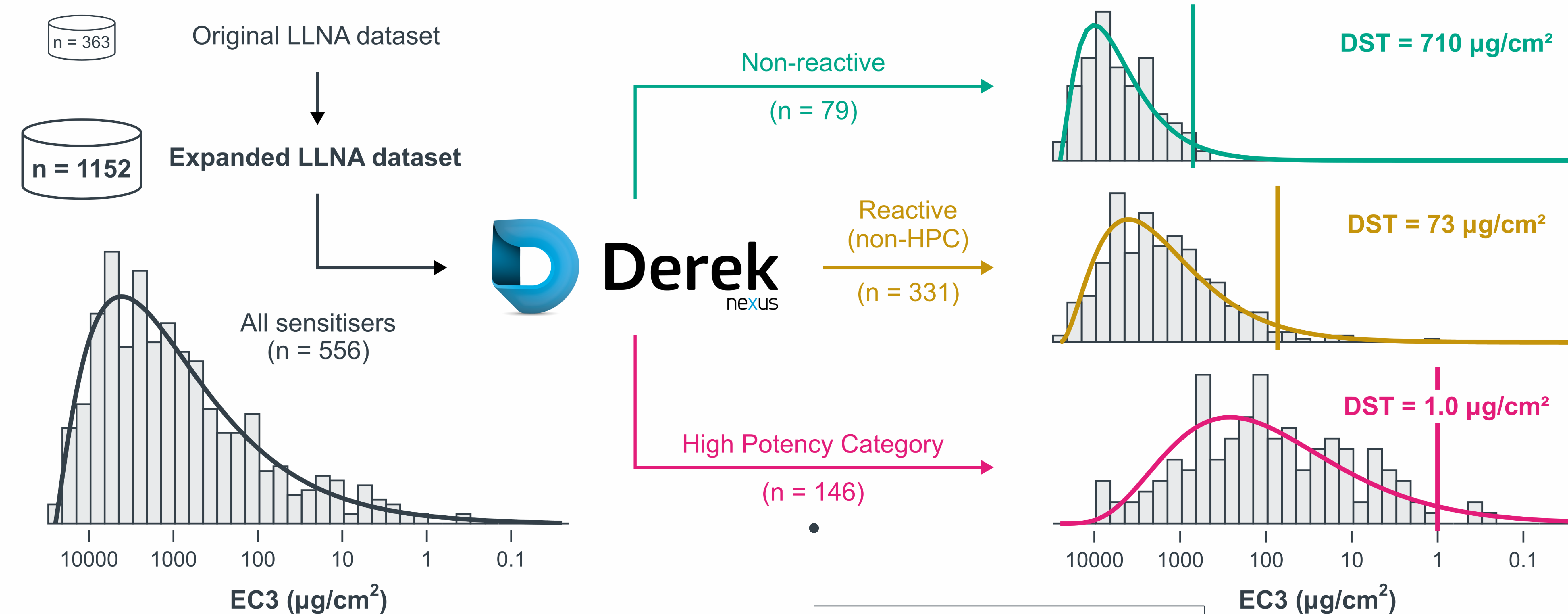
Project aim: Update the published Dermal Sensitisation Thresholds (DSTs) using an expanded Local Lymph Node Assay (LLNA) dataset and an *in silico* expert system.

- Thresholds of Toxicological Concern for skin sensitisation.^[1, 2]
- Useful thresholds in a quantitative (next-generation) risk assessment, which can support exposure-based waiving.^[3, 4]
- Non-reactive DST = 900 $\mu\text{g}/\text{cm}^2$,^[1] reactive DST = 64 $\mu\text{g}/\text{cm}^2$.^[2]
- High Potency Category (HPC) rules^[5] identify highly potent sensitisers, leading to an HPC DST = 1.5 $\mu\text{g}/\text{cm}^2$.^[6]

- Local Lymph Node Assay (LLNA) data were collected from the public domain and curated in-house.
- The expanded dataset is over three times as large as the original dataset (n = 1152 cf. 363).
- The EC3 potency values of the sensitisers in the dataset (n = 556) are still well-modelled by a gamma distribution.

- Use of Derek Nexus automates the reactivity classification, with a similarly high performance to that of a human expert.

Dataset	Classifier	Sensitivity	Specificity
Original	Human expert	86%	64%
Original	Derek Nexus	87%	61%
Expanded	Derek Nexus	85%	63%



- The updated DSTs are similar to the original values, despite being based on up to twice as many chemicals.
- The updated DSTs are highly protective of human health.

DST	Difference to original value	Change in no. of chemicals	Probability that EC3 > DST
Non-reactive	-1.3-fold	+2.1-fold	99.7%
Reactive (non-HPC)	+1.1-fold	+1.4-fold	98.2%
HPC	-1.5-fold	+1.3-fold	98.6%

Conclusions

- The expanded LLNA dataset contains three times as many chemicals as the original dataset.
- The *in silico* expert system Derek Nexus can automatically classify chemicals into a DST category.
- Updated **non-reactive DST = 710 $\mu\text{g}/\text{cm}^2$** .
- Newly derived **reactive (non-HPC) DST = 73 $\mu\text{g}/\text{cm}^2$** .
- Updated **HPC DST = 1.0 $\mu\text{g}/\text{cm}^2$** .
- The updated DSTs are similar to the published thresholds and remain protective of human health.
- It is hoped that these updated thresholds will be useful within a quantitative (next generation) risk assessment of skin sensitisation.

References

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- The HPC rules^[5] were given minor updates based on analysis of the expanded dataset and were encoded into Derek Nexus.
- The updated rules were able to filter out 86% (59/69) of the highly potent chemicals (i.e., those with an EC3 < 64 $\mu\text{g}/\text{cm}^2$).
- Using Derek's reactivity assignment, updated DST values were derived from the 95th percentile of each gamma distribution.