

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



Martyn L. Chilton^a, Donna S. Macmillan^a, Anne Marie Api^b, G. Frank Gerberick^c, Maura Lavelle^b, Mihwa Na^b, Devin O'Brien^b, Robert J. Safford^d

^a Lhasa Limited, Granary Wharf House, 2 Canal Wharf, Leeds, LS11 5PS, UK

^b Research Institute for Fragrance Materials, Inc., 50 Tice Boulevard, Woodcliff Lake, NJ, USA

^c GF3 Consultancy, LLC, West Chester, OH, USA

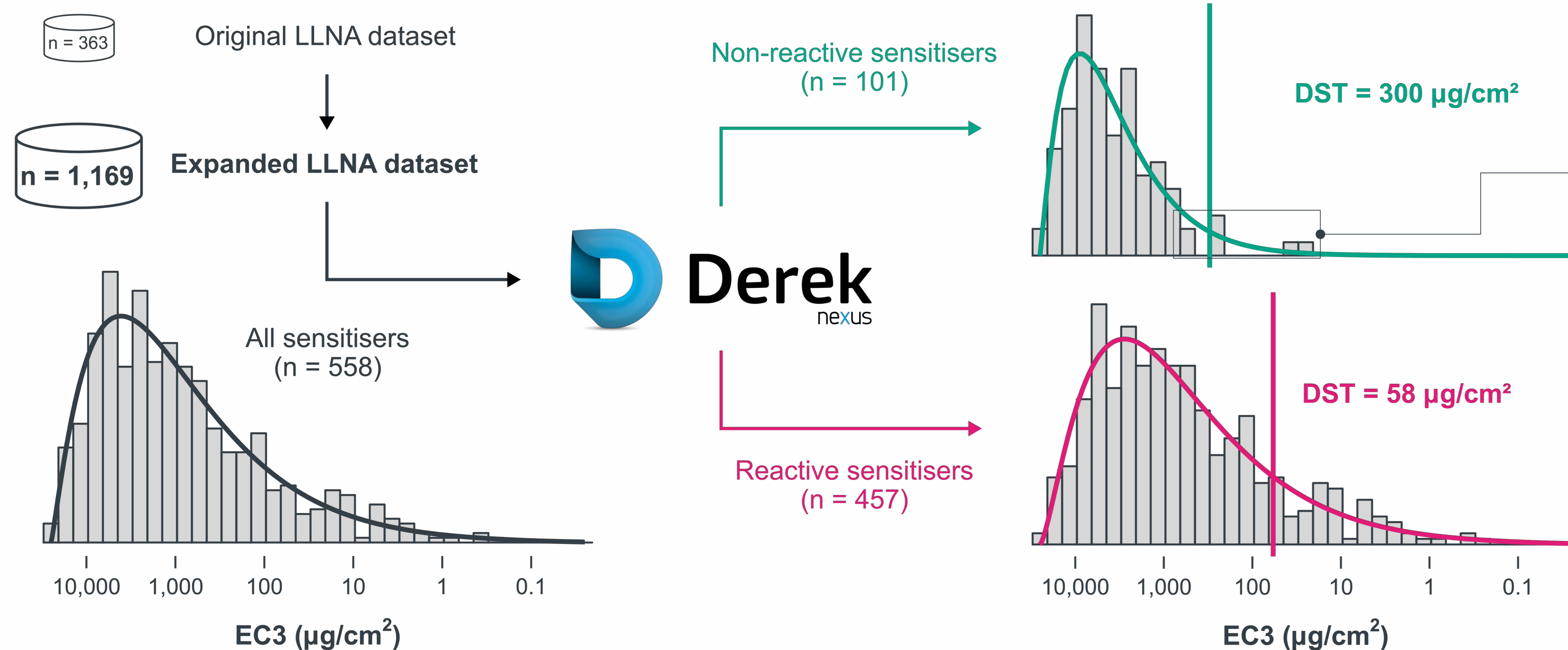
^d B-Safe Toxicology Consulting, 31 Hayway, Rushden, Northants, NN10 6AG, UK

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

- Thresholds of Toxicological Concern for skin sensitisation. [1]
- Useful in a Quantitative Risk Assessment [2] when *in vivo* and/or *in vitro* skin sensitisation data is lacking.
- Non-reactive DST = 900 $\mu\text{g}/\text{cm}^2$ [3], reactive DST = 64 $\mu\text{g}/\text{cm}^2$. [4]
- Based on an original LLNA dataset containing 363 chemicals. [3]

- Collected from the public domain and curated in-house.
- Over 3 times as large as the original dataset (n = 1,169).
- Approximately balanced prevalence (48% are sensitisers).
- The EC3 potency values of the sensitisers in the dataset (n = 558) are well-modelled using a gamma distribution.

- Use of Derek Nexus automates the reactivity classification.
- Similar performance to human experts against the original dataset (85% agreement, accuracy = 80% for both classifiers).
- Good performance is also observed against the expanded dataset (accuracy = 71%, sensitivity = 82%, specificity = 62%).



Name	EC3 ($\mu\text{g}/\text{cm}^2$)	Comments on reactivity [5]
Tris(4-(diethylamino)phenyl)methylum acetate	25	Insufficient supporting data to create a Derek alert for this class. High Potency Category (HPC) chemical due to presence of a quinone methide type Michael Acceptor (MA). [6]
Chlorpromazine	35	Possible autoxidation/metabolism to form a dialdehyde. [7] HPC chemical due to formation of a doubly activated MA. [6]
Iodopropynyl butylcarbamate	218	Insufficient supporting data to create a Derek alert for this class. Likely to be S _N 2-reactive but not an HPC chemical.
HC orange no. 2	275	Possible autoxidation/metabolism to form a dialdehyde but not an HPC chemical.
O,S-Dibutyl dithioimido decarbonate	275	Possible (pseudo-)acyl transfer agent. HPC due to structural complexities. [6]
Ascaridole	450	Possible radical reaction. [8] HPC chemical due to the presence of an organic peroxide. [6]

■ Conclusions

- An expanded LLNA dataset containing 1,169 chemicals has been collated.
- Derek Nexus (an *in silico* expert system) can be used to classify skin sensitisation reactivity.
- At present, the **non-reactive DST** is **300 $\mu\text{g}/\text{cm}^2$** . This is 3 times smaller than the original value and is based on over 2.5 times as many chemicals.
- At present, the **reactive DST** is **58 $\mu\text{g}/\text{cm}^2$** . This is very similar to the original value, despite being based on twice as many chemicals.
- Analysis of the dataset is ongoing. Upon completion, the finalised updated DSTs will be published.

References

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