



# Dermal Sensitisation Thresholds as an *in silico* tool within a toxicological risk assessment

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# Outline

- Background
  - Skin sensitisation
  - Lhasa Limited's *in silico* models
  - Dermal Sensitisation Thresholds
- Updating the Dermal Sensitisation Thresholds
  - Using *in silico* models to predict reactivity
  - Expanding the LLNA dataset
  - Handling highly potent sensitisers
  - Updating the DST values
- Summary and conclusions

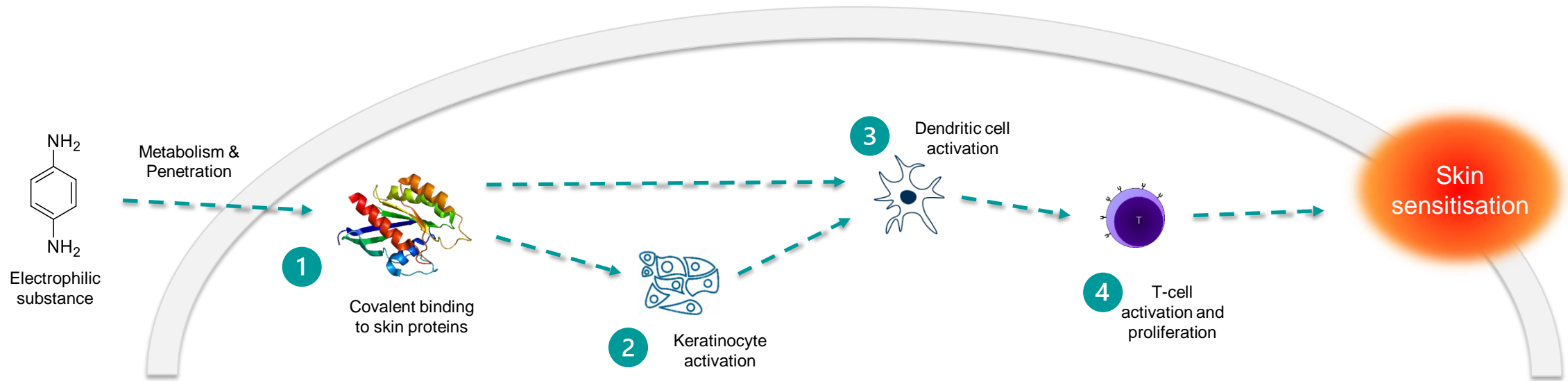




**Background**

# Skin sensitisation: what is it?

- An allergic response caused by repeated exposure to a particular chemical
  - ~20% of the general population are thought to be allergic to at least 1 chemical
  - Common allergens include nickel, fragrances and hair dye ingredients
- Has a simple and relatively well-understood Adverse Outcome Pathway (AOP)



Thyssen et al, *Contact Dermatitis* **2007**, 57, 287-299

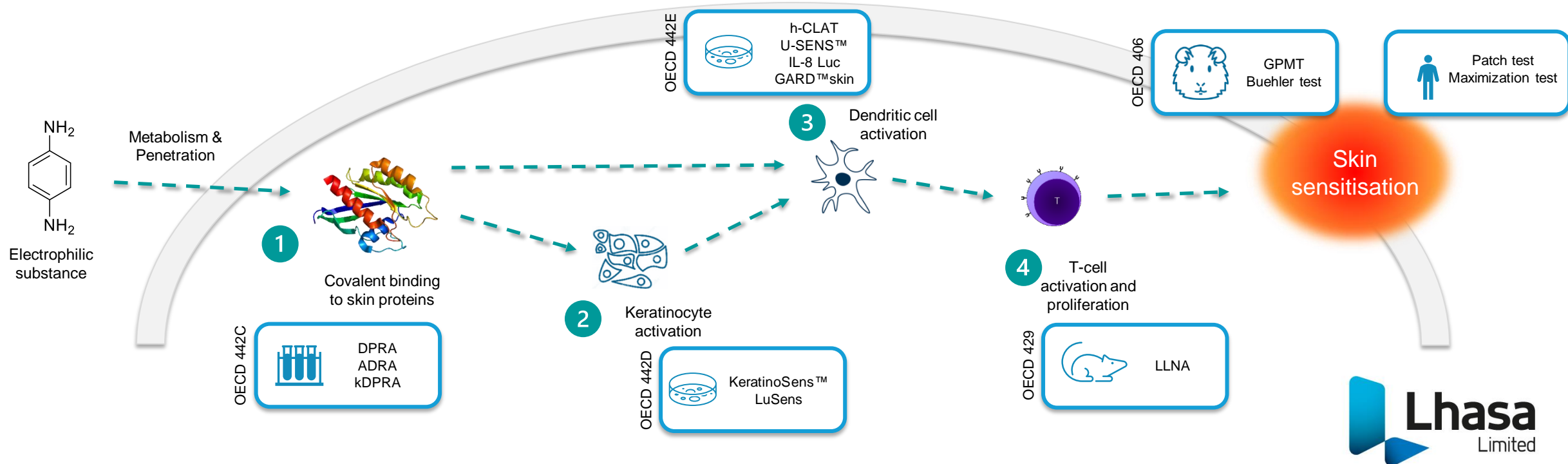
Peiser et al, *Cell. Mol. Life. Sci.* **2012**, 69, 763-781

Figure adapted from OECD 2012, The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins Part 1:

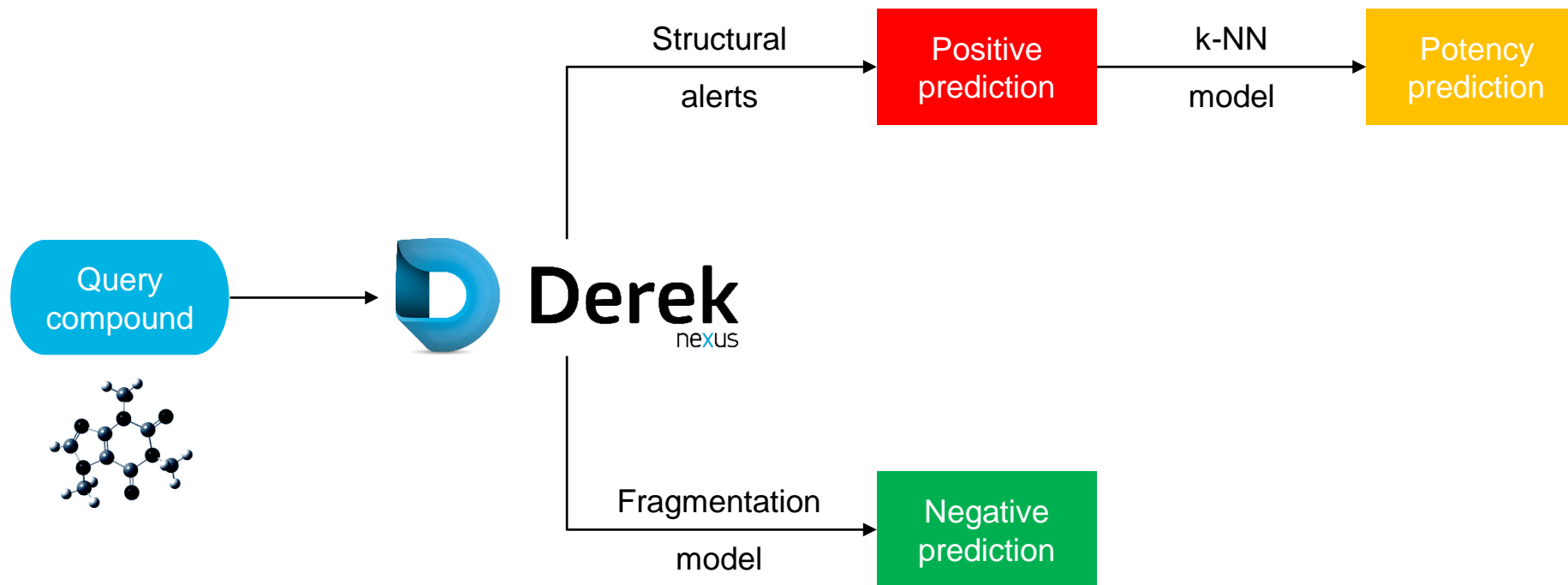
Scientific Evidence, Series on Testing and Assessment, No. 168.

# Skin sensitisation: how is it assessed?

- Historically assessed using animal models
  - Multiple drivers for replacing these: ethical, financial, legal, scientific, social
- Many alternatives to animal assays have been developed
  - Each assay is linked to a different key event in the AOP



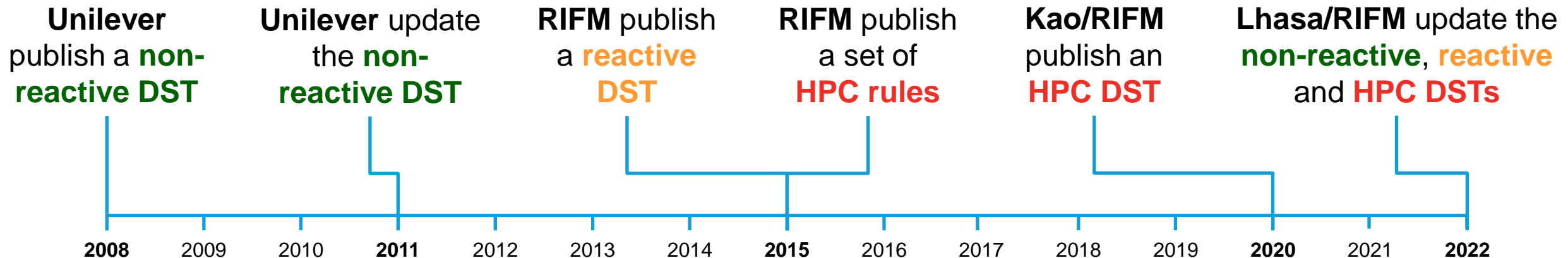
# Lhasa's *in silico* sensitisation models



- SAR knowledge for skin sensitisation predates the *in chemico/in vitro* approaches
- Describe toxicophores by combining data, mechanism and chemical principals
- Continually improved by analysing public and proprietary data

# Dermal Sensitisation Thresholds (DSTs)

- DSTs are Thresholds of Toxicological Concern for skin sensitisation
  - If a chemical's exposure is below the relevant DST, sensitisation is very unlikely
- They have been iteratively developed over the past 15 years
  - Unilever, RIFM and Kao have all played key roles in their creation and use



# Where are the DSTs used?



- **Personal care products**

- *“Some ingredients, such as colours, may be used at low levels in products, leading to very low dermal exposure, particularly from a rinse-off product.”*



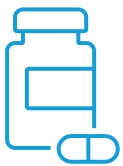
- **Fragrance materials**

- *“QRA2 does not apply where... proposed levels of use of a fragrance material result in exposures that are below the Dermal Sensitization Threshold”*



- **Cosmetic ingredients**

- *“In the absence of existing hazard data, exposure-based waiving can be applied within a risk assessment.”*

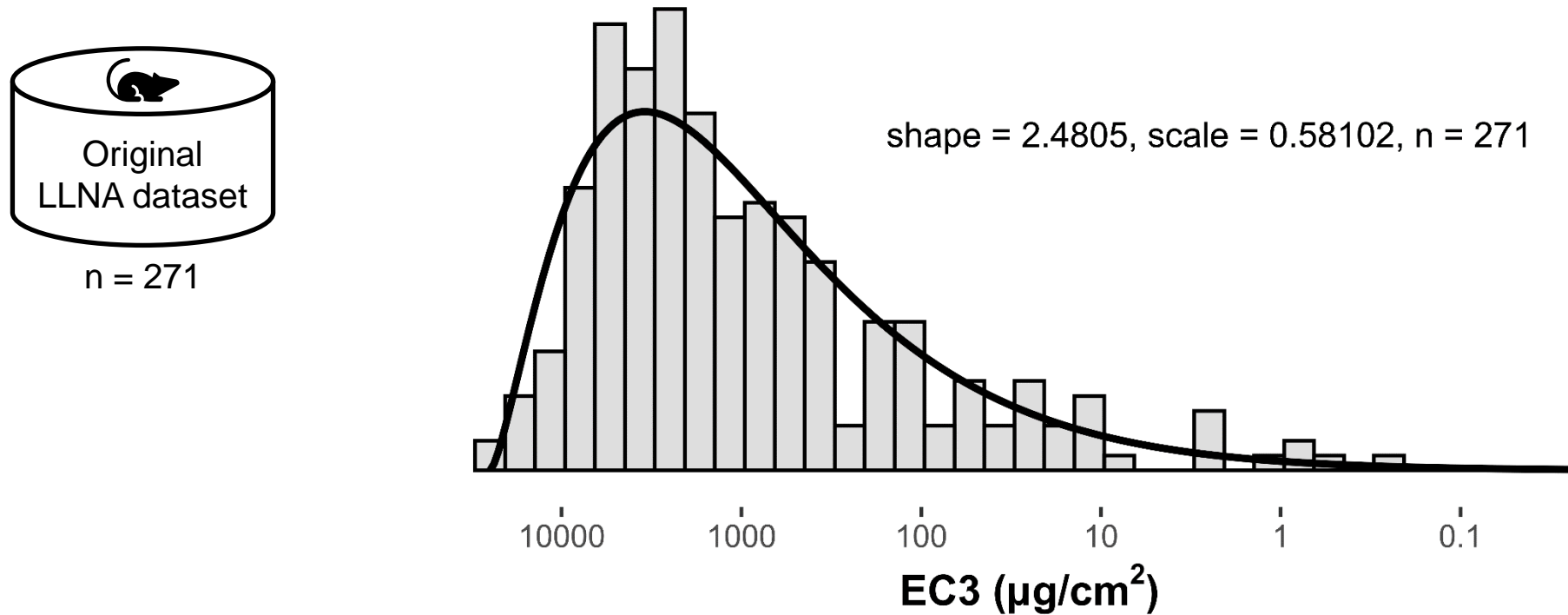


- **Pharmaceutical products**

- *“The DST approach... is considered appropriate for the sensitisation risk assessment of potential leachables in topical pharmaceutical products”*

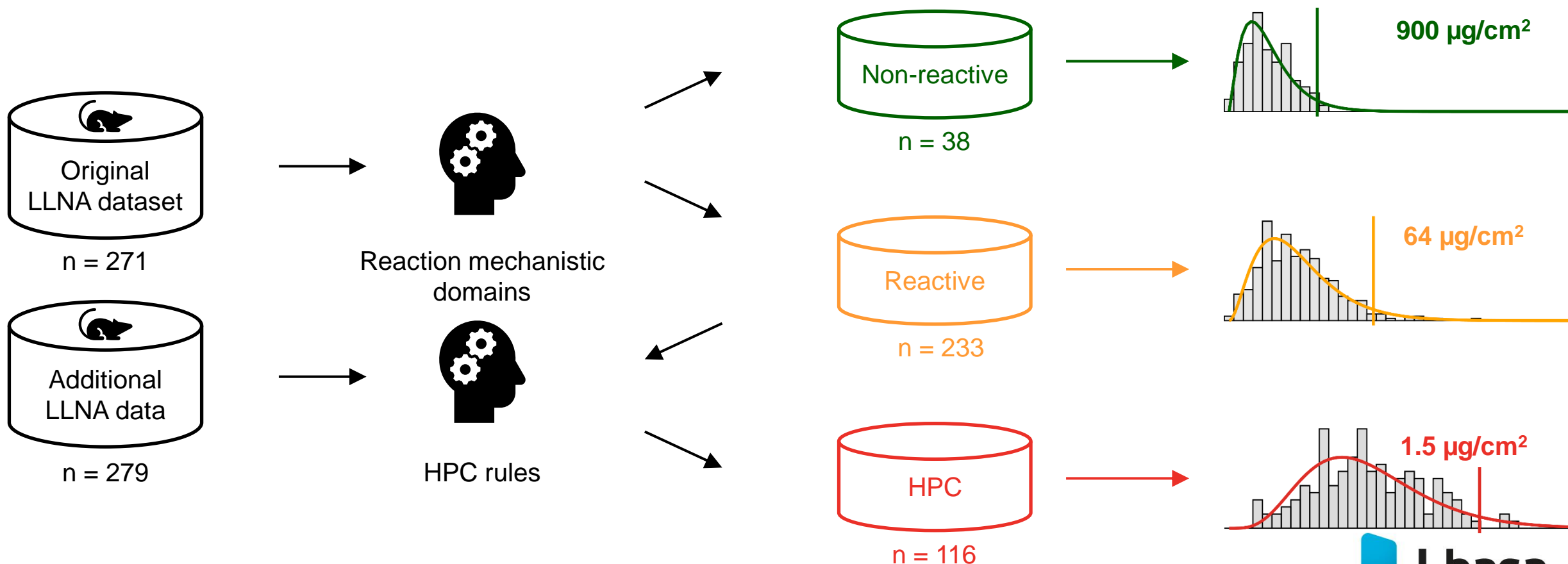
# How are the DSTs derived?

- Data-driven by using a gamma distribution to estimate safe thresholds



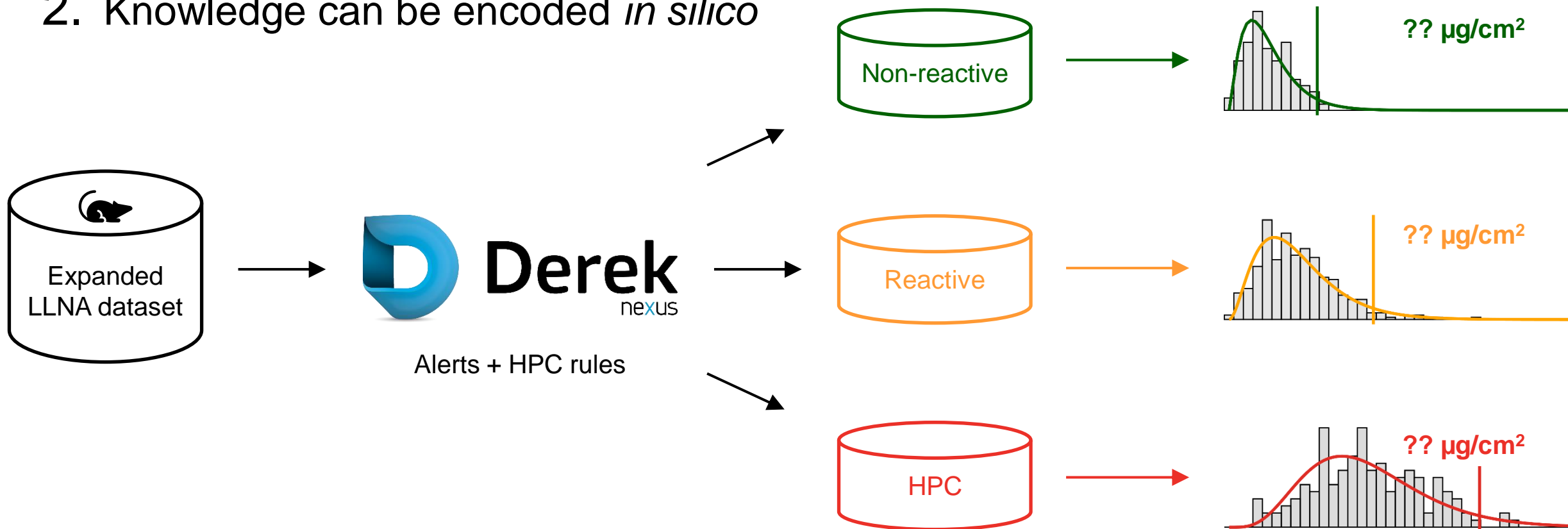
# How are the DSTs derived?

- Data-driven by using a gamma distribution to estimate safe thresholds



# Why update the DSTs?

1. More LLNA data is now available
2. Knowledge can be encoded *in silico*



- Will the updated DSTs remain robust and protective?



# Updating the DSTs

# Using *in silico* models to predict reactivity

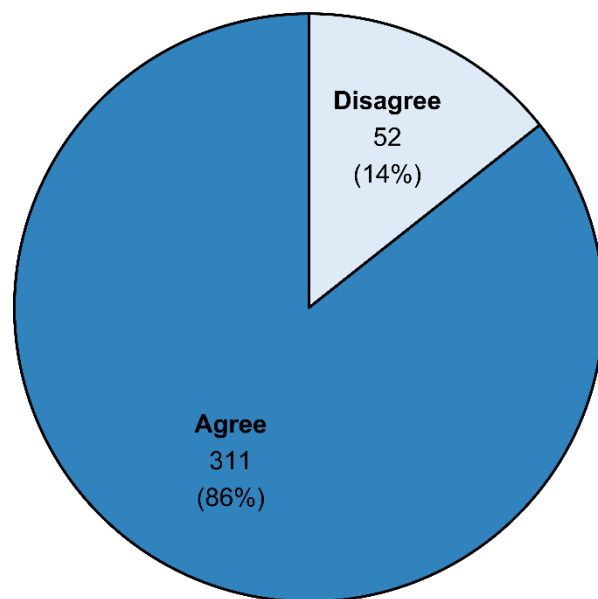
- Derek performed similarly well to a human expert

Comparison between human and *in silico* reactivity classifiers



Original LLNA dataset

n = 363



Derek Nexus domain classification

		Acyl	MA	SB	S <sub>N</sub> 2	S <sub>N</sub> Ar	Misc, Multiple, Radical
Human expert domain classification	Acyl	21		1			1 2
	MA		39	3	2		43 4
	SB			38	1		4 2
	S <sub>N</sub> 2	1			46	1	4 3
	S <sub>N</sub> Ar					3	1
	Complex, Multiple, Special case		1			3	6 11

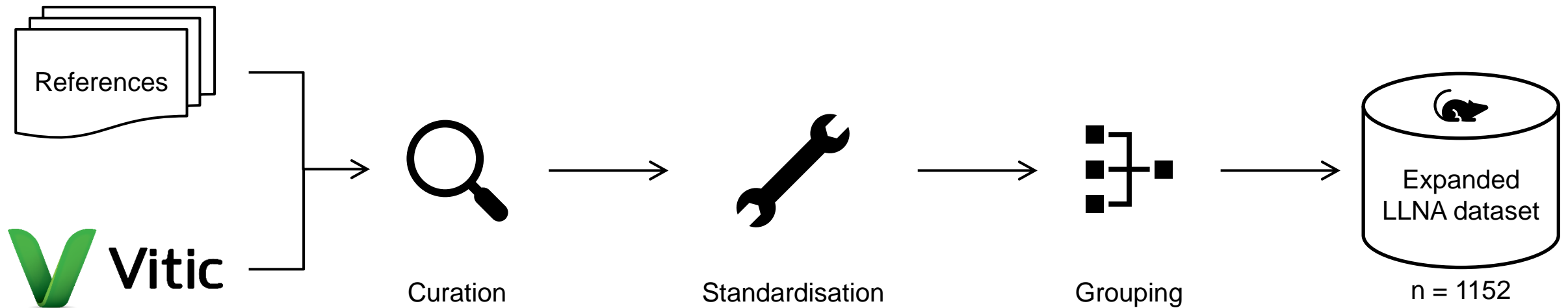
Reactivity classifier	Accuracy	Sensitivity	Specificity	Balanced accuracy	Reactive DST	Non-reactive DST
Human expert	80%	86%	64%	75%	64 µg/cm <sup>2</sup>	900 µg/cm <sup>2</sup>
Derek Nexus	80%	87%	61%	74%	77 µg/cm <sup>2</sup>	930 µg/cm <sup>2</sup> <sup>a</sup>

<sup>a</sup> After removing the false positive hexyl salicylate



# Expanding the LLNA dataset

- Publicly available LLNA data was collected and curated in-house



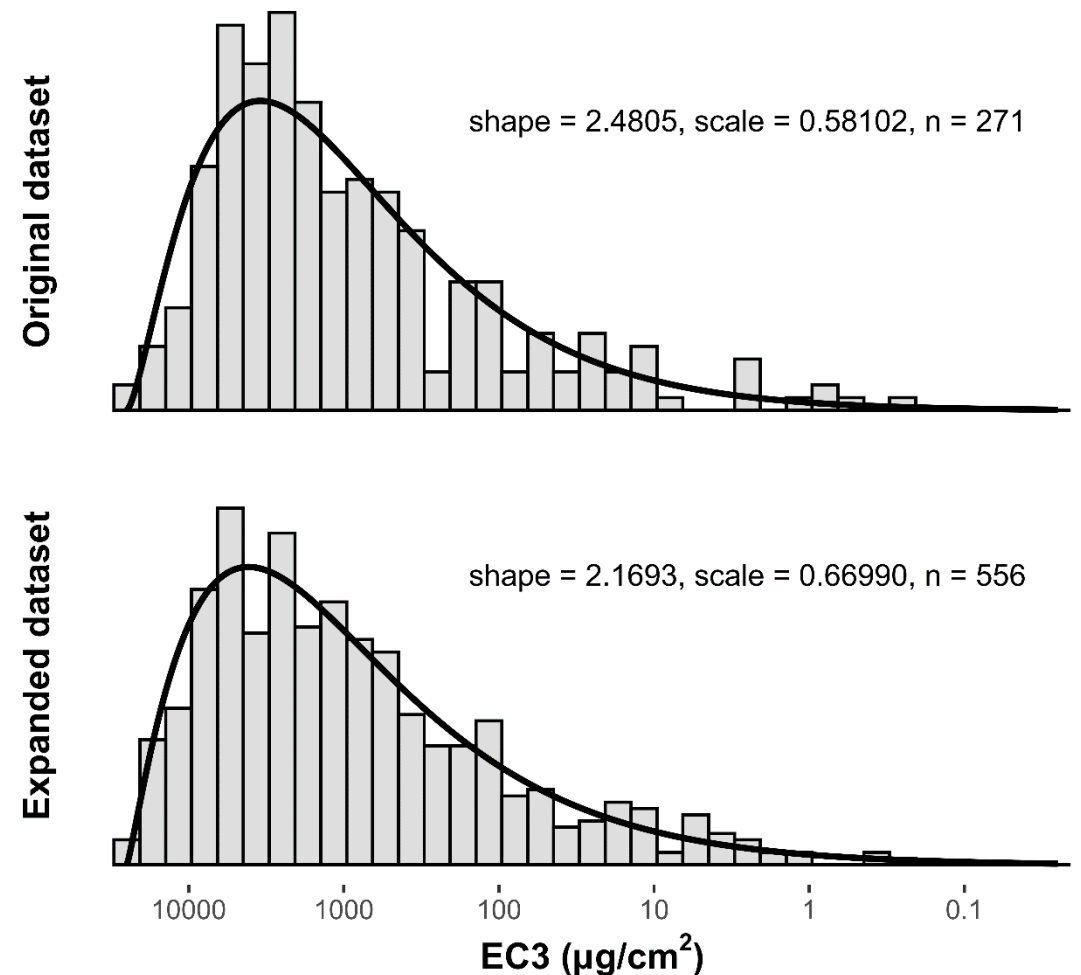
- Each sensitiser is associated with a single EC3 value
  - Chemicals with mixed activity conservatively assigned as sensitisers
  - Median EC3 value used where multiple positive LLNA studies available

# Expanding the LLNA dataset

- **Size:** over 3 times larger
  - Original dataset:  $n = 363$
  - Expanded dataset:  $n = 1152$
- **Prevalence:** more balanced
  - Original dataset: 75% sensitisers
  - Expanded dataset: 48% sensitisers
- **Derek performance:** very similar

Dataset	Accuracy	Sensitivity	Specificity	Balanced accuracy
Original	80%	87%	61%	74%
Expanded	73%	85%	63%	74%

- **EC3 distribution:** very similar



# Handling highly potent sensitisers

- The HPC rules were designed to highlight extremely potent structural features
  - Each set of rules is linked to a specific reactive mechanistic domain

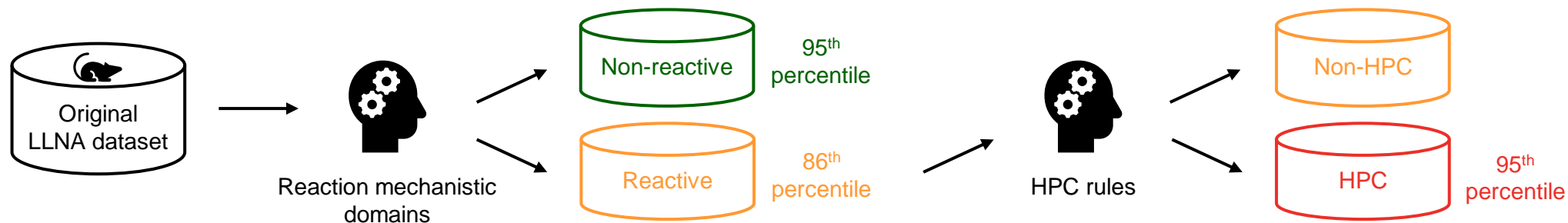
Rule	Mechanistic domain	Rule	Mechanistic domain	Rule	Mechanistic domain
1	Protein derivatising agents	4	Schiff base electrophiles	7	S <sub>N</sub> Ar electrophiles
2	Direct acting Michael acceptors	5	Acyl transfer agents	8	Organic peroxides
3	Pro/pre-Michael acceptors	6	S <sub>N</sub> 2 electrophiles	9	Structurally complex chemicals

- Minor updates to the rules were made, based on the expanded dataset
- The updated HPC rules were then encoded into Derek Nexus
  - Same classification as a human expert 92% of the time
  - 86% of the extremely potent sensitisers were identified by Derek as HPC
  - Common differences for subjective rule 9, which is difficult to encode

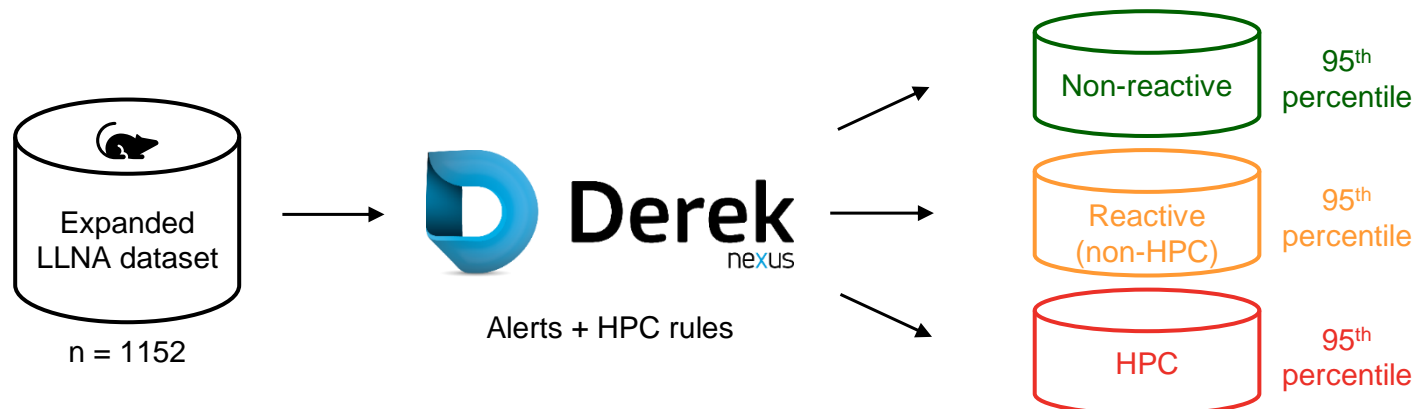


# Handling highly potent sensitisers

- The HPC rules were designed as a belt-and-braces approach
  - Filter out very potent chemicals to after assigning chemical reactivity

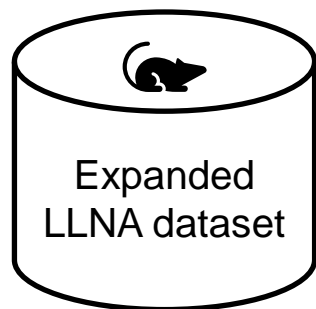


- Instead, could they be used upfront to separate the HPC chemicals?
  - This would lead to the derivation of the three DSTs all based on the 95<sup>th</sup> percentile

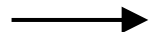


# Updating the DST values

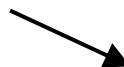
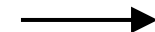
- Bringing it all together...



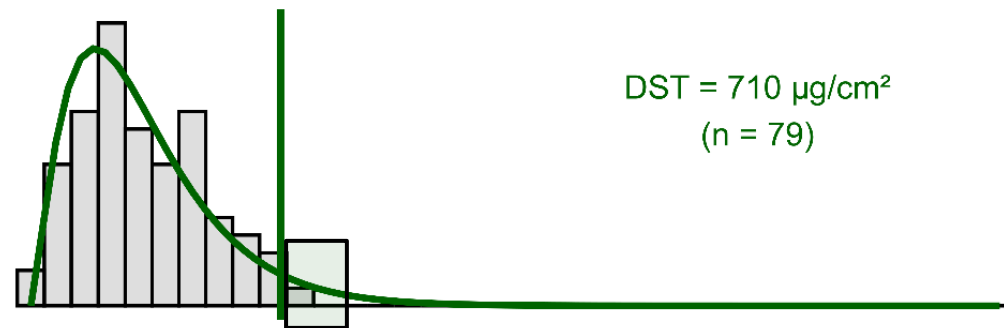
n = 1152



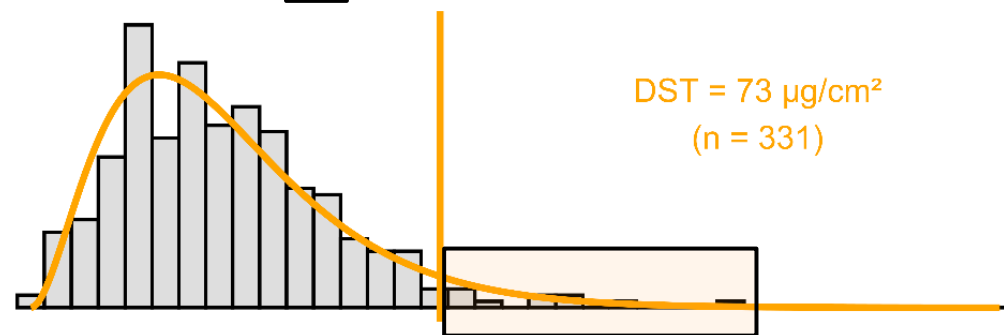
Alerts + HPC rules



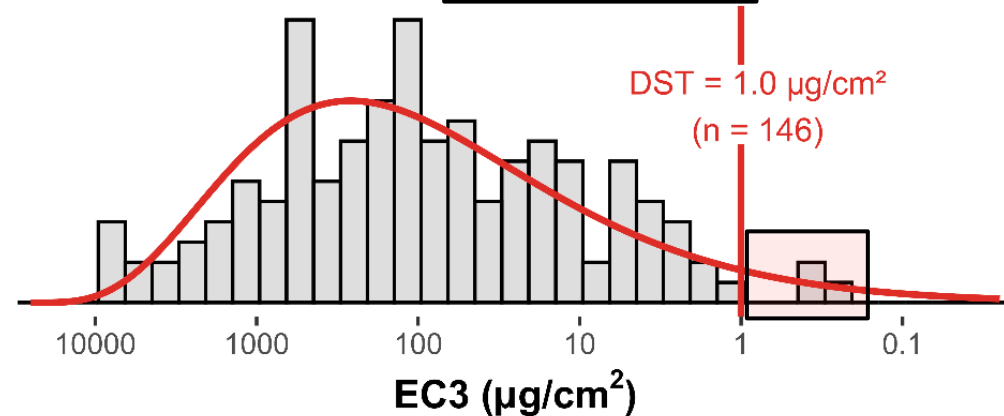
Non-reactive



Reactive  
(non-HPC)



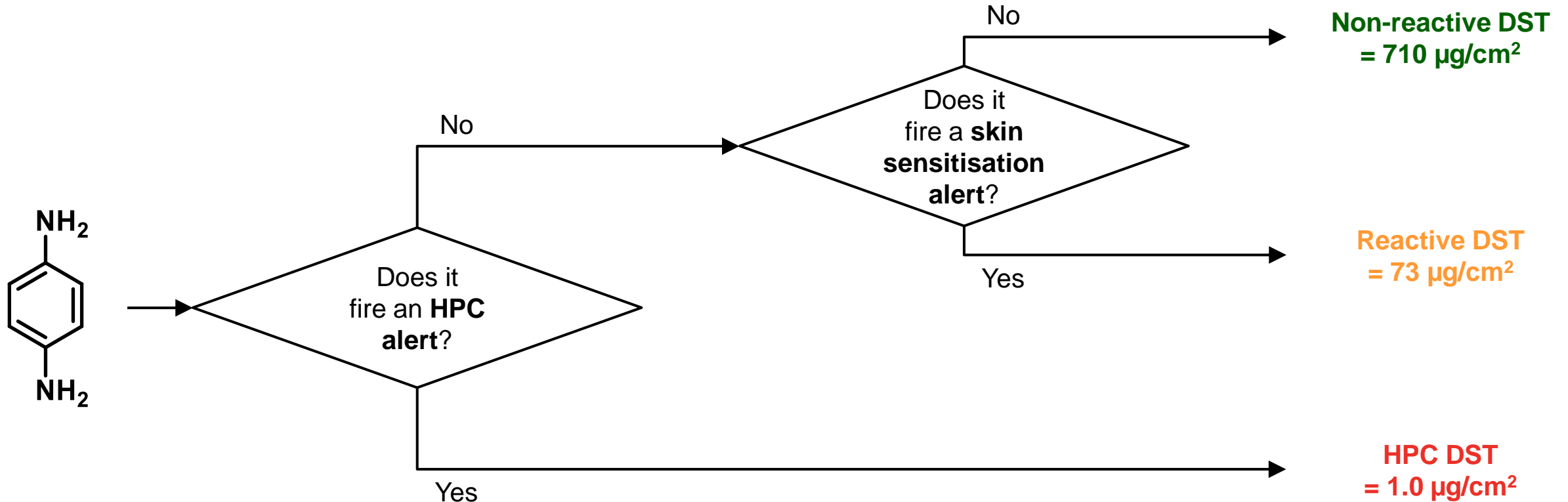
HPC



EC3 ( $\mu\text{g}/\text{cm}^2$ )

# Updating the DST values

- Simple decision tree approach in Derek:

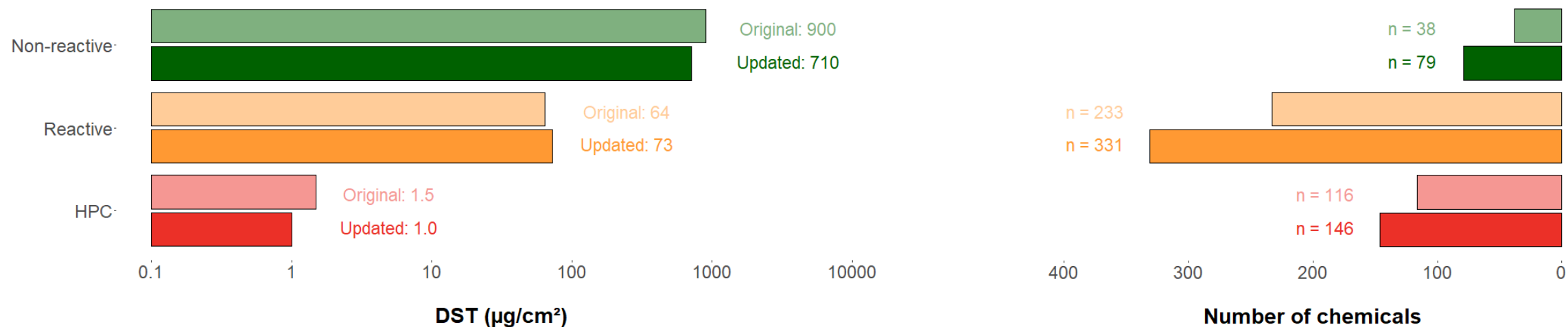




# **Summary and conclusions**

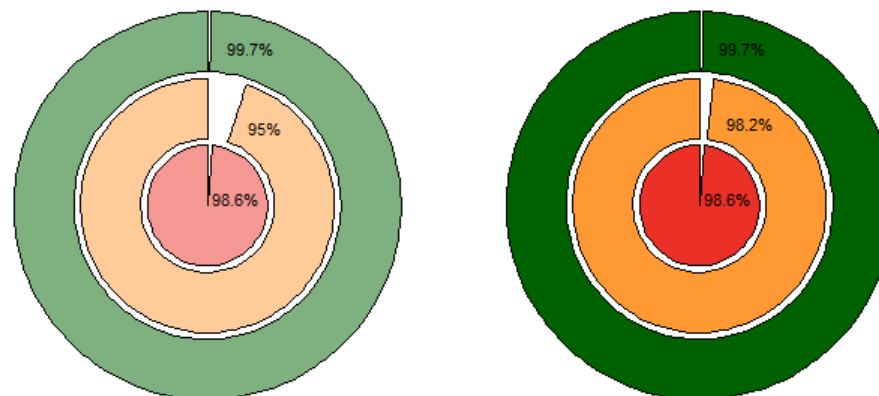
# Summary

- The updated DSTs are very similar to the previously published values



- The updated DSTs remain highly protective of human health

Probability of a chemical having an EC3 > DST:



# Conclusions

- Conclusions
  - Derek Nexus can be used to classify skin sensitisation reactivity and HPC
  - The expanded dataset has a similar distribution but contains 2x as many sensitisers
  - The additional LLNA data allowed for some minor updates to the HPC rules
  - The updated DSTs remain robust and highly protective of human health
- Outcomes
  - The research has been published in *Regulatory Toxicology and Pharmacology*
  - The updated knowledge is available in Derek Nexus v6.2
  - Potential for case studies to increase confidence in the approach

# Acknowledgements



- Catherine O'Leary-Steele
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- Mihwa Na



# Thanks for listening

Any questions?

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