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

3rd *In Silico* Toxicology Conference

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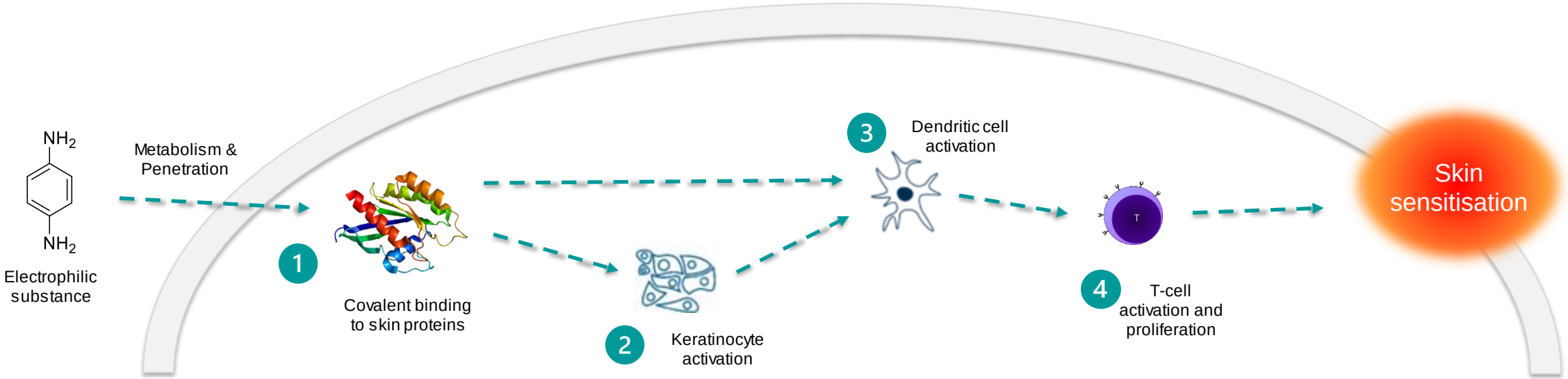
Outline

- 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.

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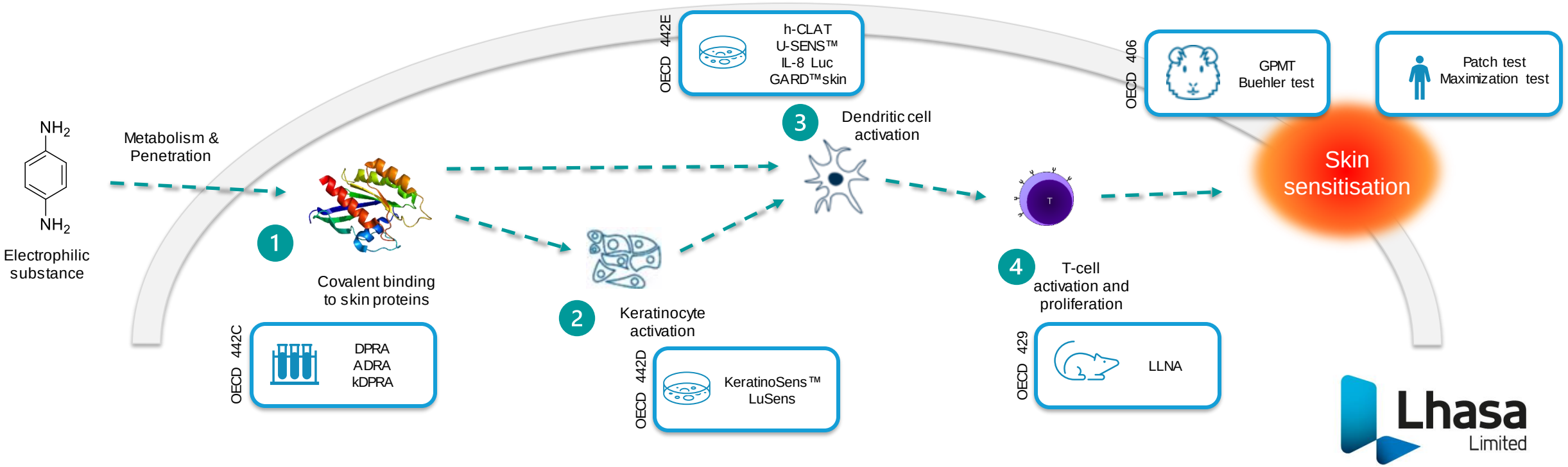
Skin sensitisation: how is it assessed?

- 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



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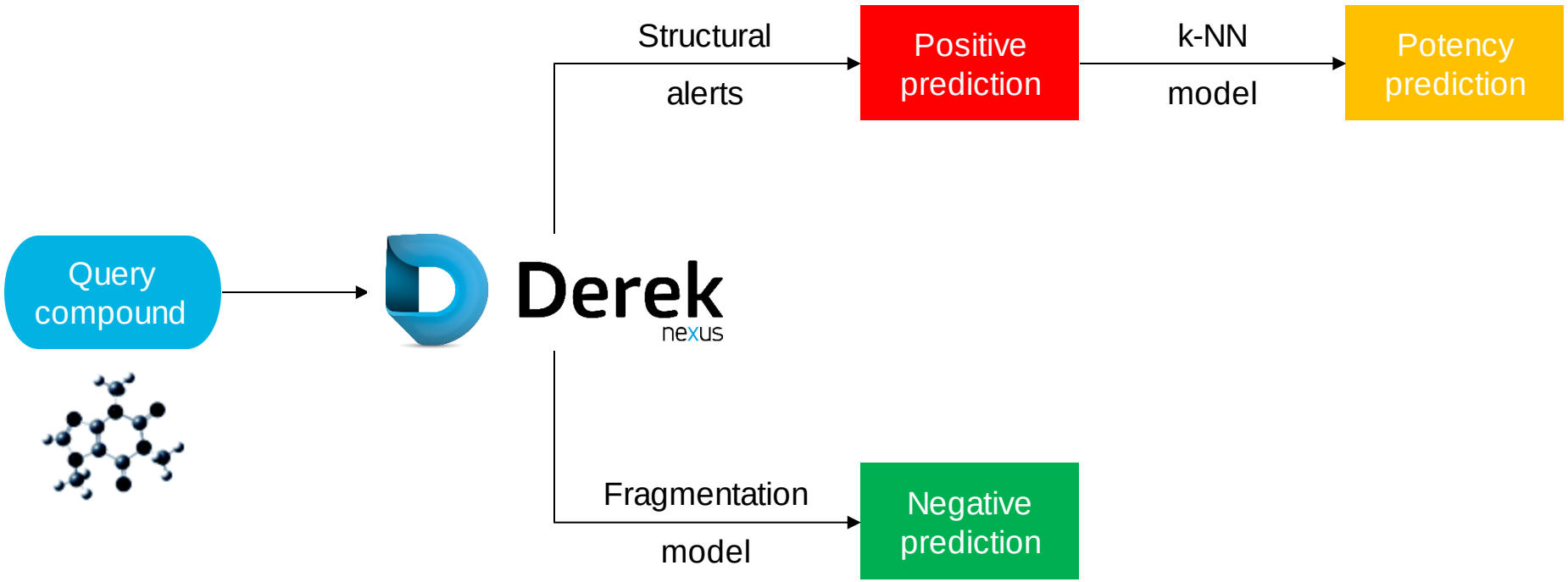
Lhasa's *in silico* sensitisation models



- 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

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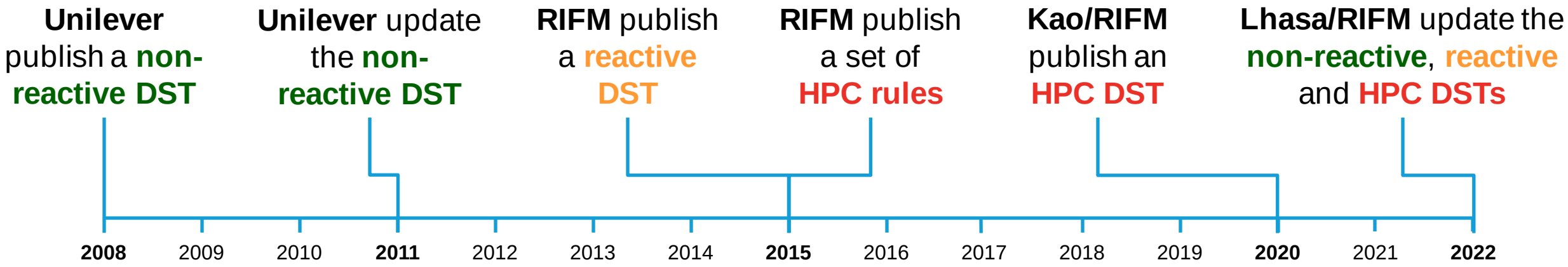
Barratt et al., *Toxicol. in Vitro* **1994**, *8*, 837-839
Macmillan et al., *Regul. Toxicol. Pharmacol.* **2022**, manuscript submitted

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



Safford, *Regul. Toxicol. Pharmacol.* **2008**, *51*, 195–200
Safford et al., *Regul. Toxicol. Pharmacol.* **2011**, *60*, 218–224
Safford et al., *Regul. Toxicol. Pharmacol.* **2015**, *72*, 694–701
Roberts et al., *Regul. Toxicol. Pharmacol.* **2015**, *72*, 683–693
Nishijo et al., *Regul. Toxicol. Pharmacol.* **2020**, *117*, 104732
Chilton et al., *Regul. Toxicol. Pharmacol.* **2022**, *133*, 105200

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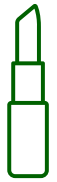
Where are the DSTs used?

- **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"*

Safford, *Regul. Toxicol. Pharmacol.* **2008**, *51*, 195–200
Api et al., *Regul. Toxicol. Pharmacol.* **2020**, *118*, 104805
Gilmour et al., *Regul. Toxicol. Pharmacol.* **2020**, *116*, 104721
Parris et al., *Crit. Rev. Toxicol.* **2022**, *52*, 125–138

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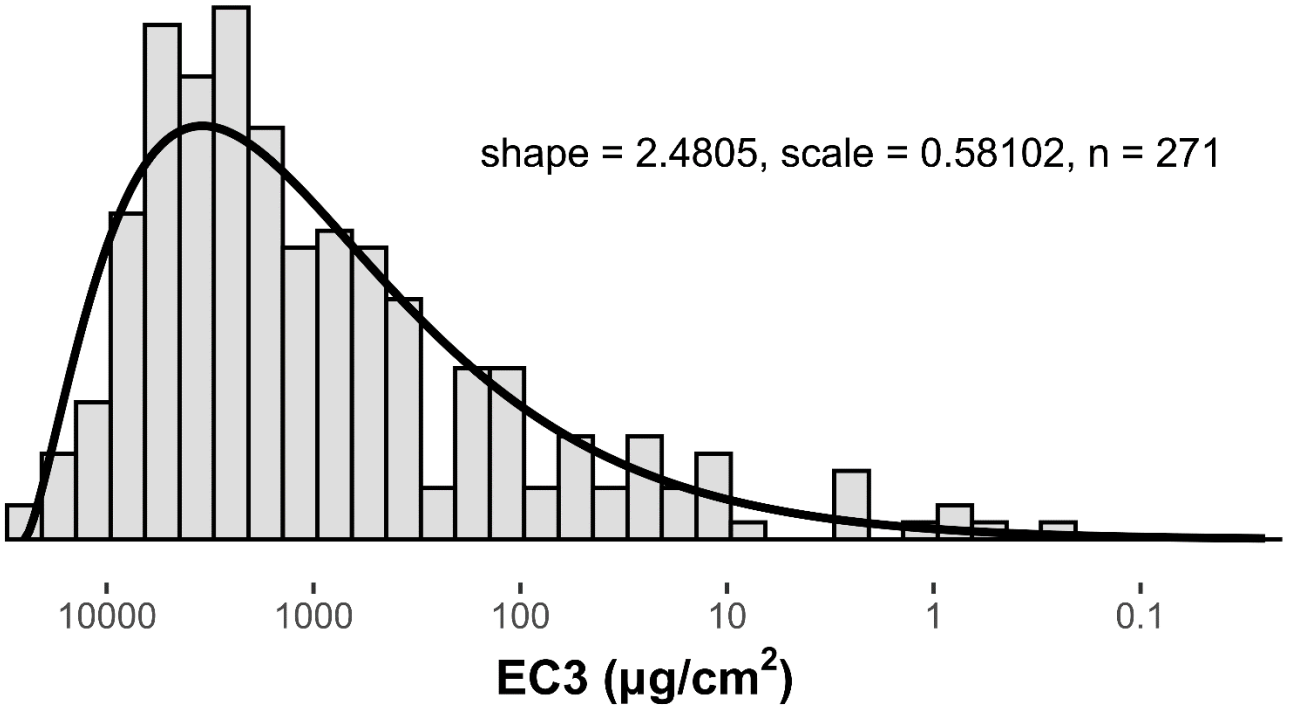
How are the DSTs derived?

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

n = 271



Safford et al., *Regul. Toxicol. Pharmacol.* **2011**, *60*, 218–224

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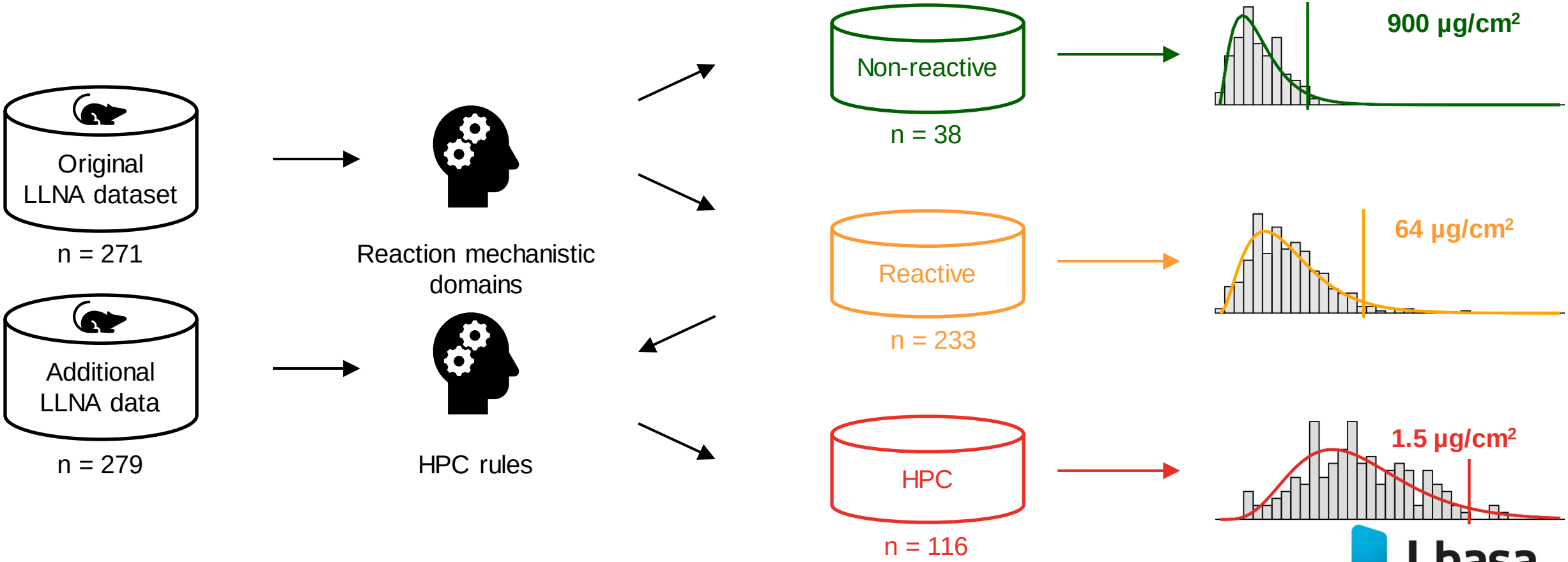

Aptula et al., *Chem. Res. Toxicol.* **2005**, *18*, 1420–1426
Safford et al., *Regul. Toxicol. Pharmacol.* **2011**, *60*, 218–224
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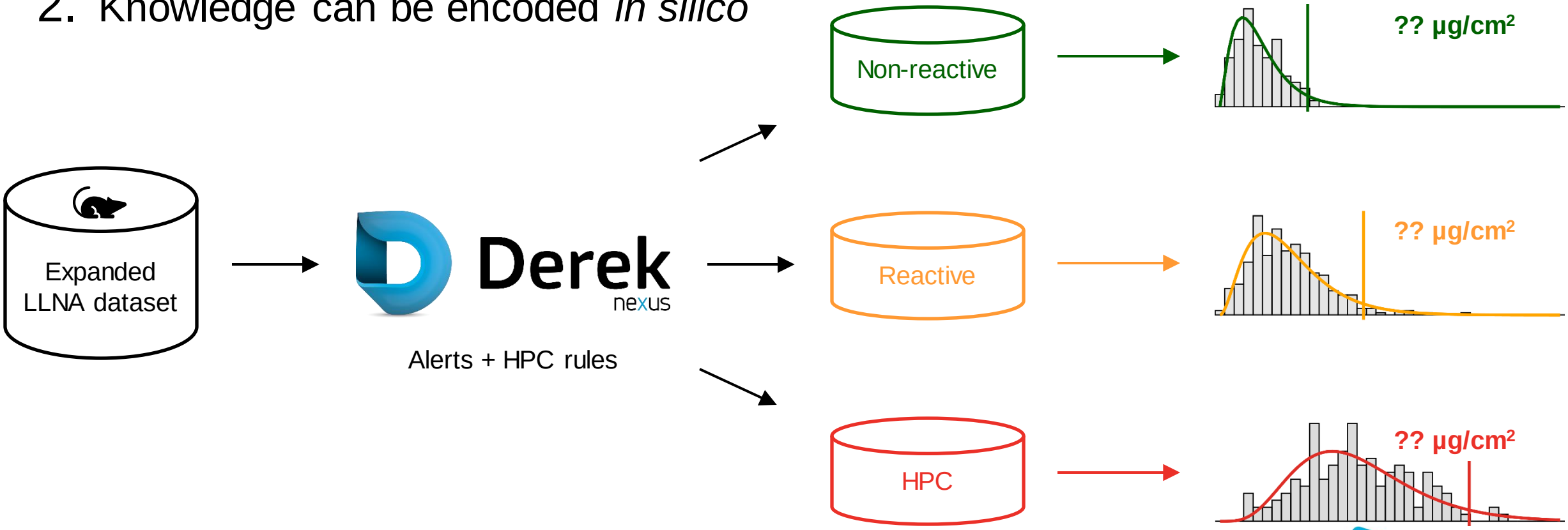
Why update the DSTs?

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



- Will the updated DSTs remain robust and protective?

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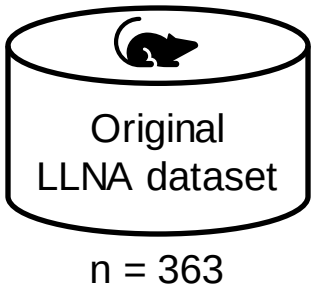
Updating the DSTs

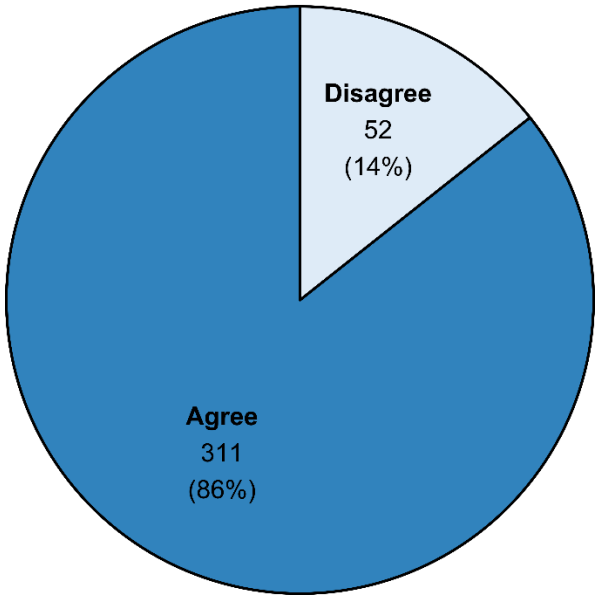
Using *in silico* models to predict reactivity

- Derek performed similarly well to a human expert



n = 363

Comparison between human and *in silico* reactivity classifiers



Derek Nexus domain classification

Human expert domain classification	Acyl	MA	SB	S_N2	S_NAr	Misc, Multiple, Radical
Acyl	21		1			1 / 2
MA		39	3	2		43 / 4
SB			38	1		4 / 2
S_N2	1			46	1	4 / 3
S_NAr					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^2	900 µg/cm^2
Derek Nexus	80%	87%	61%	74%	77 µg/cm^2	930 µg/cm^2 [a]

[a] After removing the false positive hexyl salicylate

Roberts and Api, *Regul. Toxicol. Pharmacol.* **2018**, *96*, 76–84

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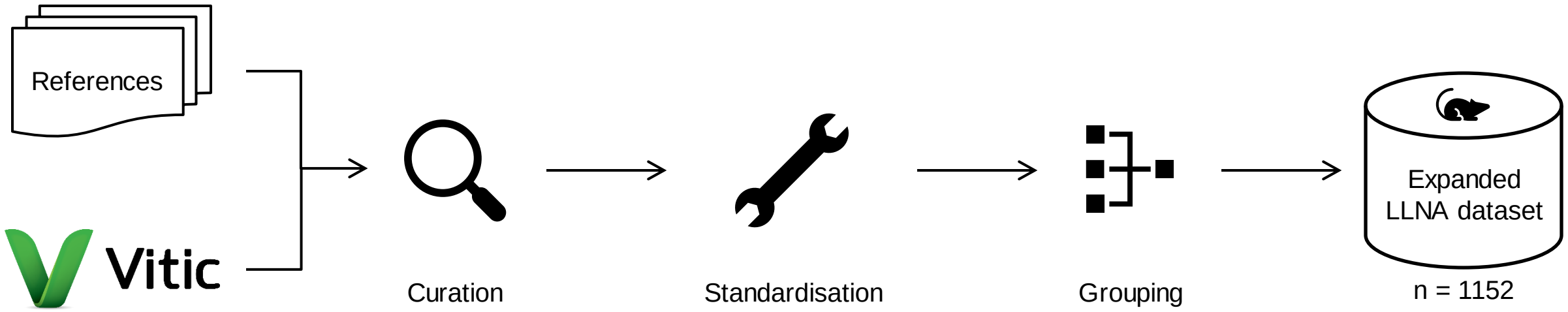
Expanding the LLNA dataset

- 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

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Expanding the LLNA dataset

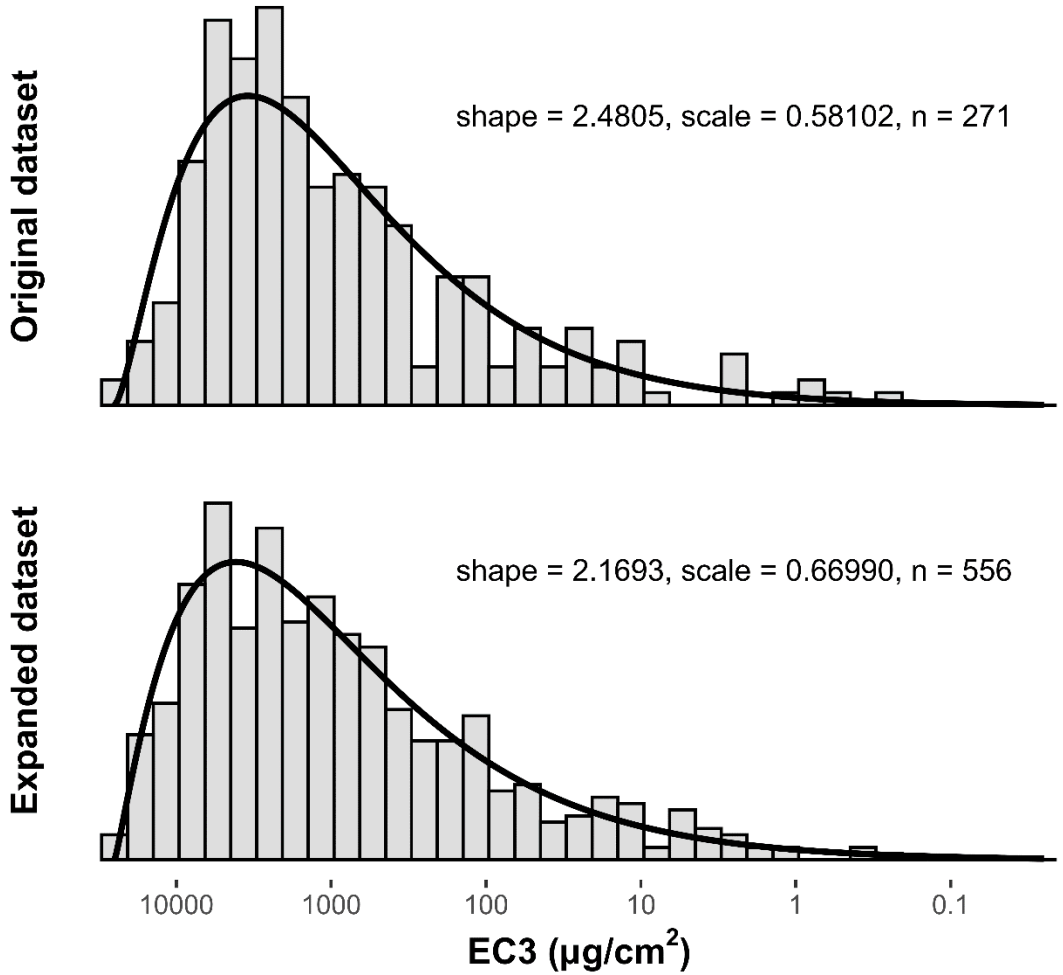
- **Size**: over 3 times larger
  - Original dataset: n = 363
  - Expanded dataset: n = 1152

- **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_NAr electrophiles
2	Direct acting Michael acceptors	5	Acyl transfer agents	8	Organic peroxides
3	Pro/pre-Michael acceptors	6	S_N2 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

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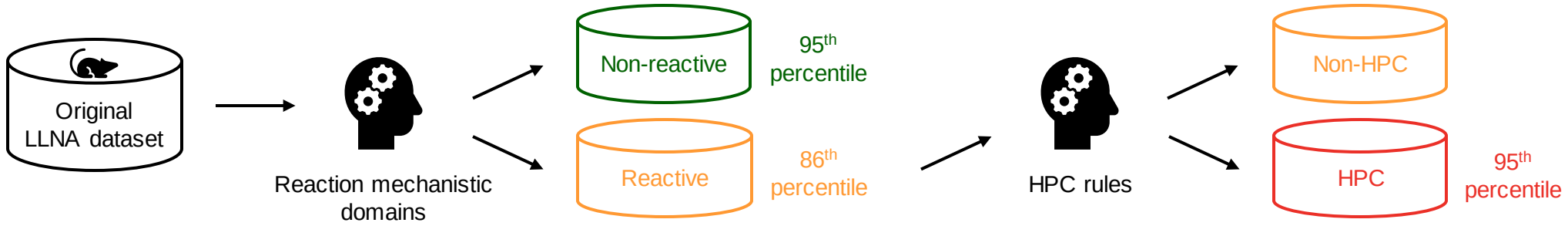
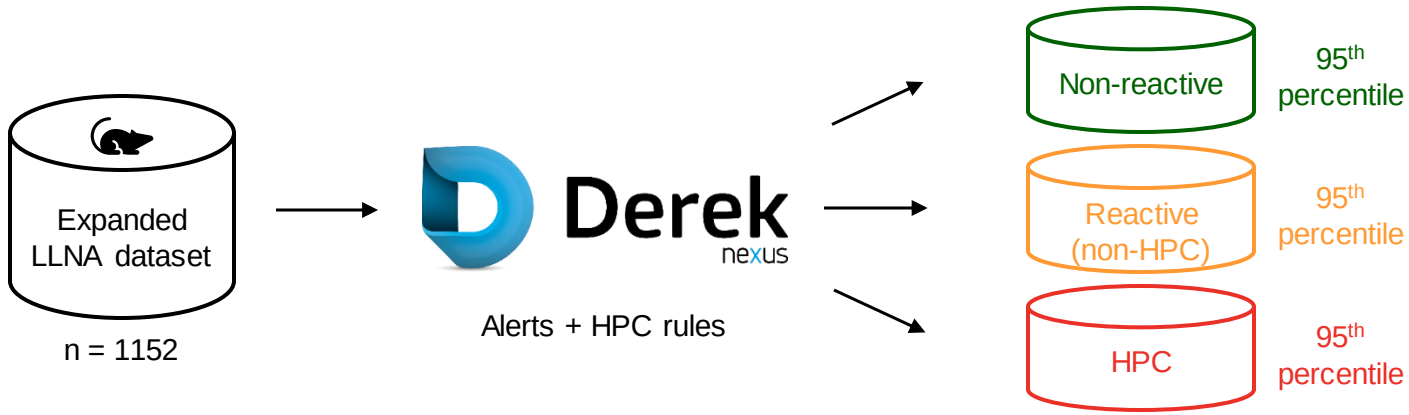
Roberts et al., *Regul. Toxicol. Pharmacol.* **2015**, *72*, 683–693

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 95th percentile



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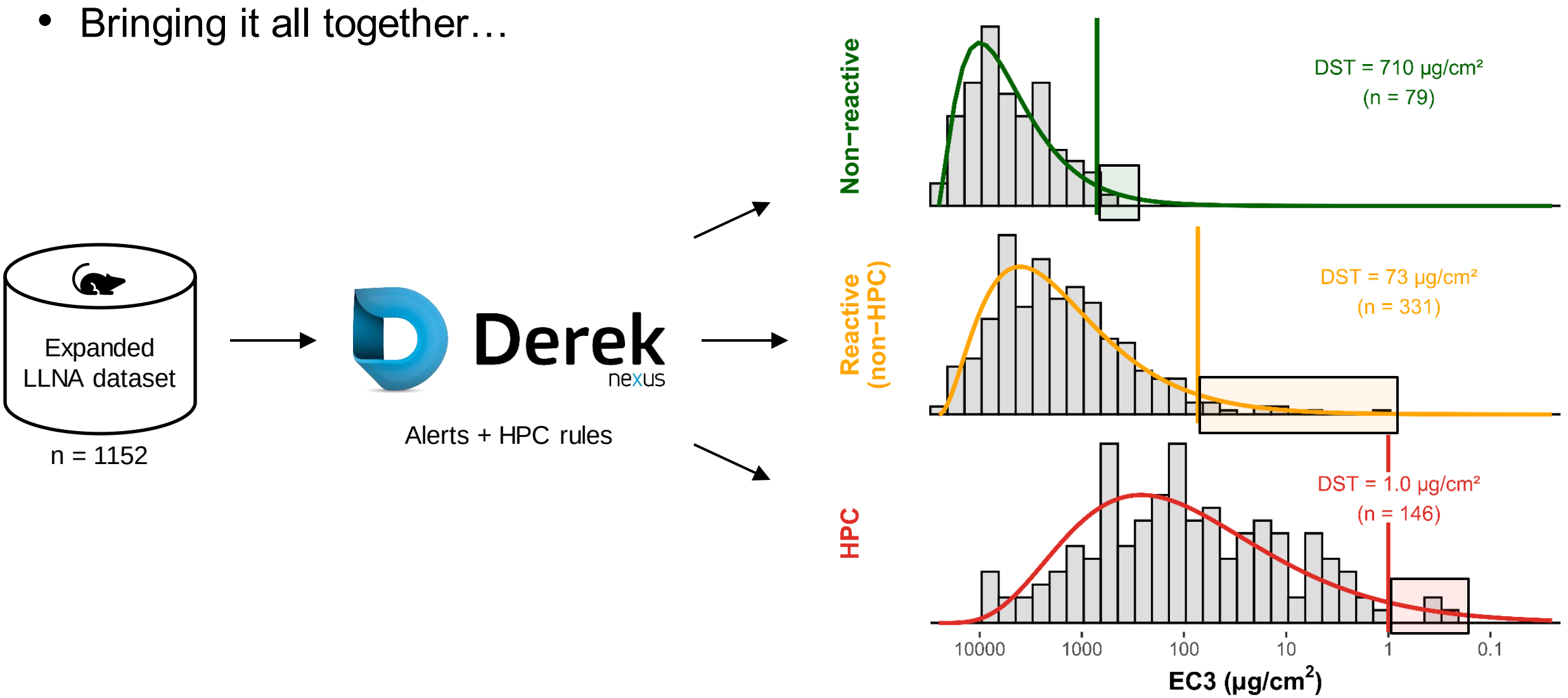
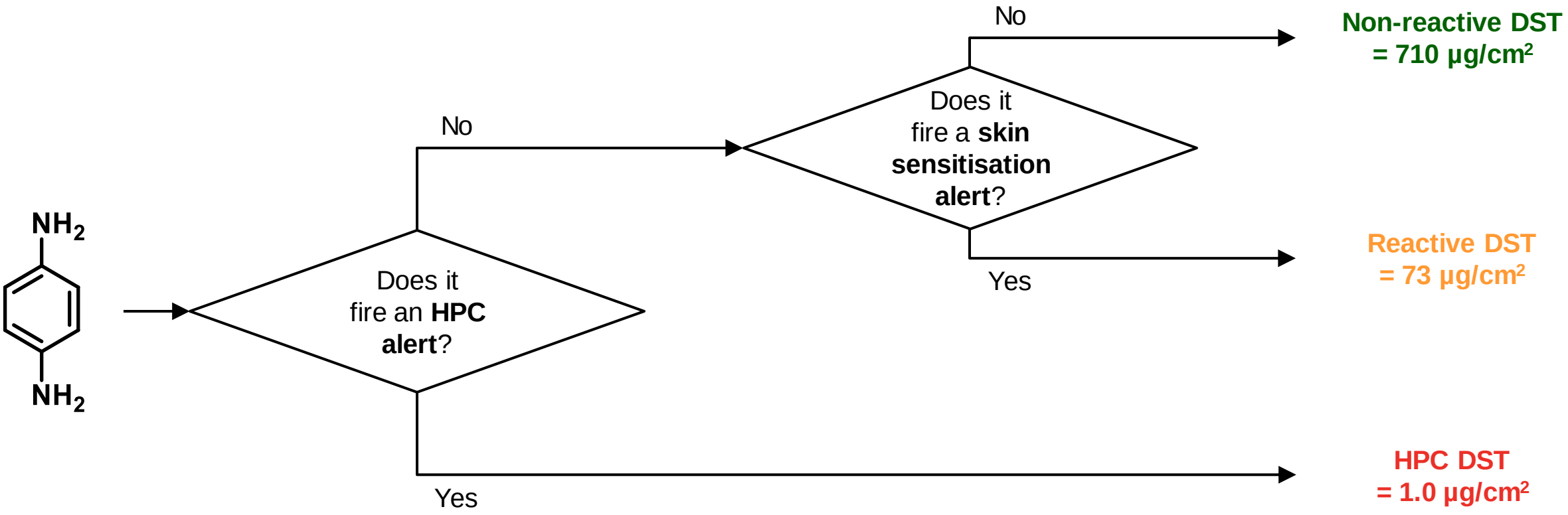
Updating the DST values

- Bringing it all together…



Updating the DST values

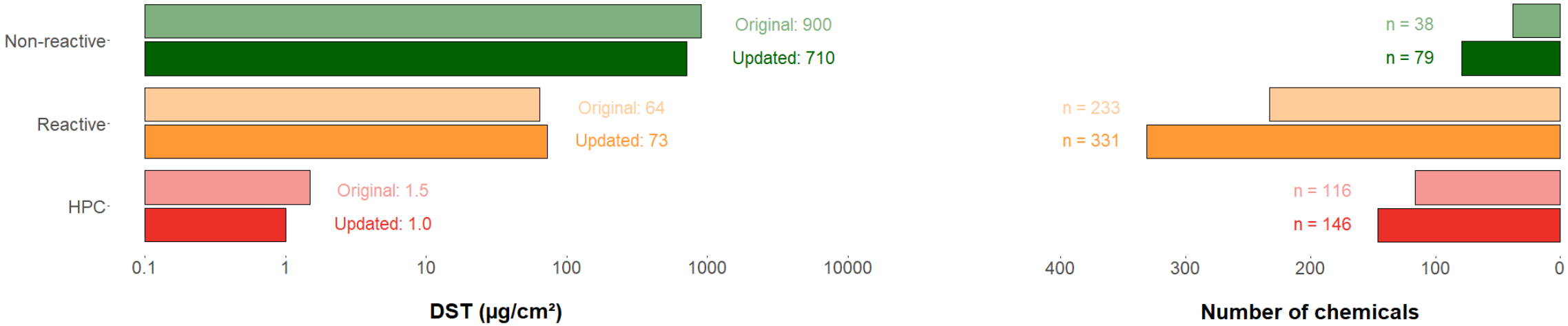
- Simple decision tree approach in Derek:



Summary and conclusions

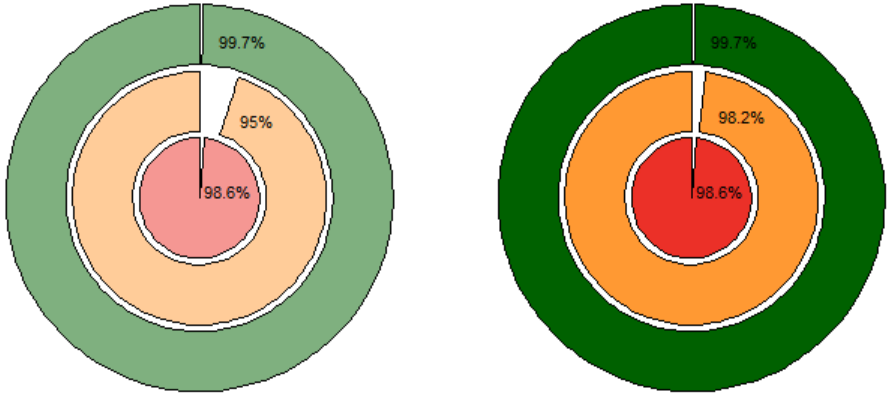
Summary

- 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:



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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

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Acknowledgements

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- Frank Gerberick (consultant)
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- Mihwa Na

Thanks for listening

Any questions?

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

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