



A defined approach for predicting skin sensitisation hazard and potency

based on the guided integration of *in silico*, *in chemico* and *in vitro* data using exclusion criteria

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Agenda

- Skin sensitisation
 - Where does Derek Nexus fit in the skin sensitisation AOP?
- Lhasa's defined approach
 - Exclusion criteria
 - Decision tree
 - Examples
 - Conclusions



Where does Derek fit in the AOP?

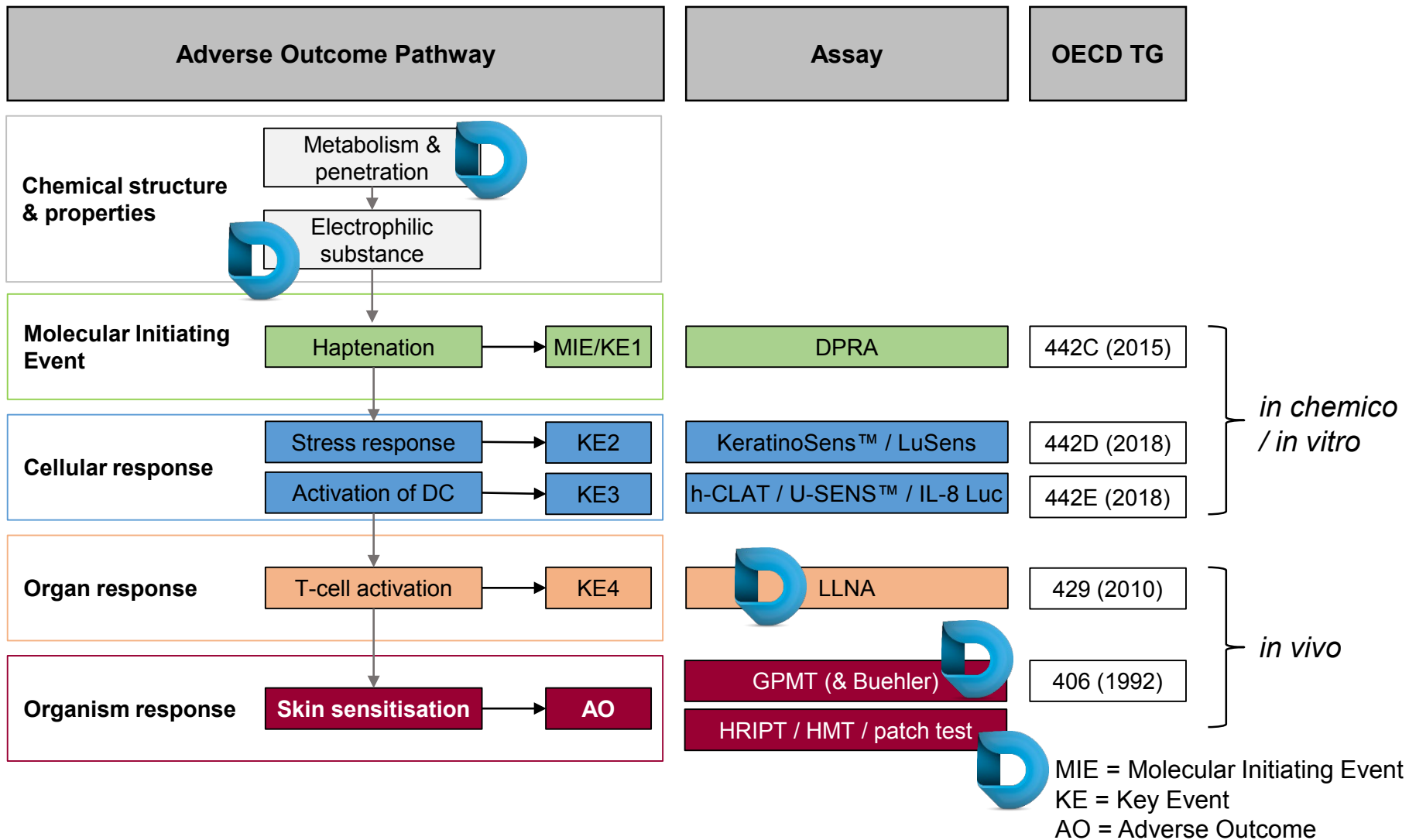


Figure adapted from OECD 2012, The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins Part 1: Scientific Evidence, Series on Testing and Assessment, No. 168.

Lhasa's hypothesis

- Apply **exclusion criteria** to chemicals based on known assay limitations and confidence in Derek predictions
- Ensures the **most relevant** information source(s) are used for a given chemical (class)
- Use Derek and assay(s) measuring the relevant KE until a concordant result is obtained - or a 2 out of 3 majority call

Pre-MIE
KE4
AO



MIE

DPRA

KE2

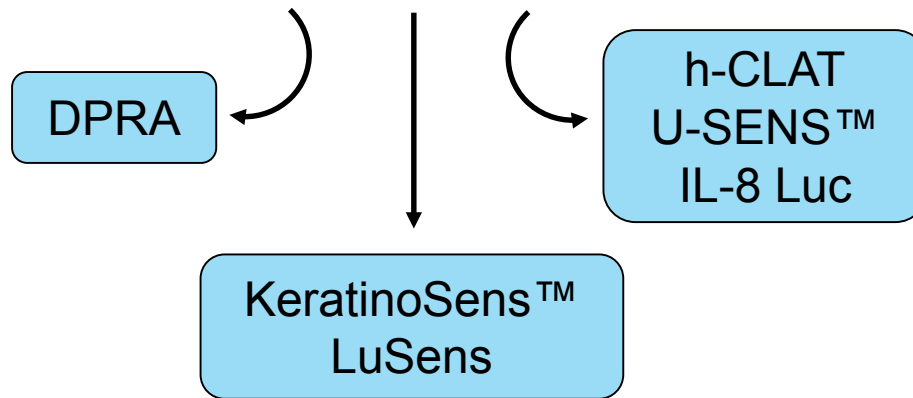
KeratinoSens™
LuSens

KE3

h-CLAT
U-SENS™
IL-8 Luc

MIE = molecular initiating event
KE = Key Event
AO = adverse outcome

Exclusion criteria



Exclusion criteria

Exclusion criteria		Derek	MIE	KE2	KE3	Comment
Metabolism	Prohaptens	✓	✗	✓	✓	Assays lacking metabolic competency are deprioritised as they are less likely to predict prohaptens well
logP	> 3.5	✓	✓	✓	✗	Cell-based assays are deprioritised for chemicals with a logP > 3.5 (KE3) and logP > 5 (KE2) as more lipophilic chemicals may lack high solubility in these cell-based assays
	> 5	✓	✓	✗	✗	
Lysine reactive	Exclusive	✓	✓	✗	✓	The Nrf2-ARE pathway is associated with cysteine binding - lysine-reactive chemicals may not be reliably predicted
Reasoning level	Equivocal	✗	N/A			Alerts with a likelihood of equivocal have less evidence of skin sensitisation potential than other likelihoods (e.g. certain) and are thus deprioritised
Negative prediction	Misclassified features	✗	N/A			Negative predictions with 'misclassified features' or 'unclassified features' are deprioritised as these are associated with higher uncertainty.
	Unclassified features	✗	N/A			

Hazard prediction

Query

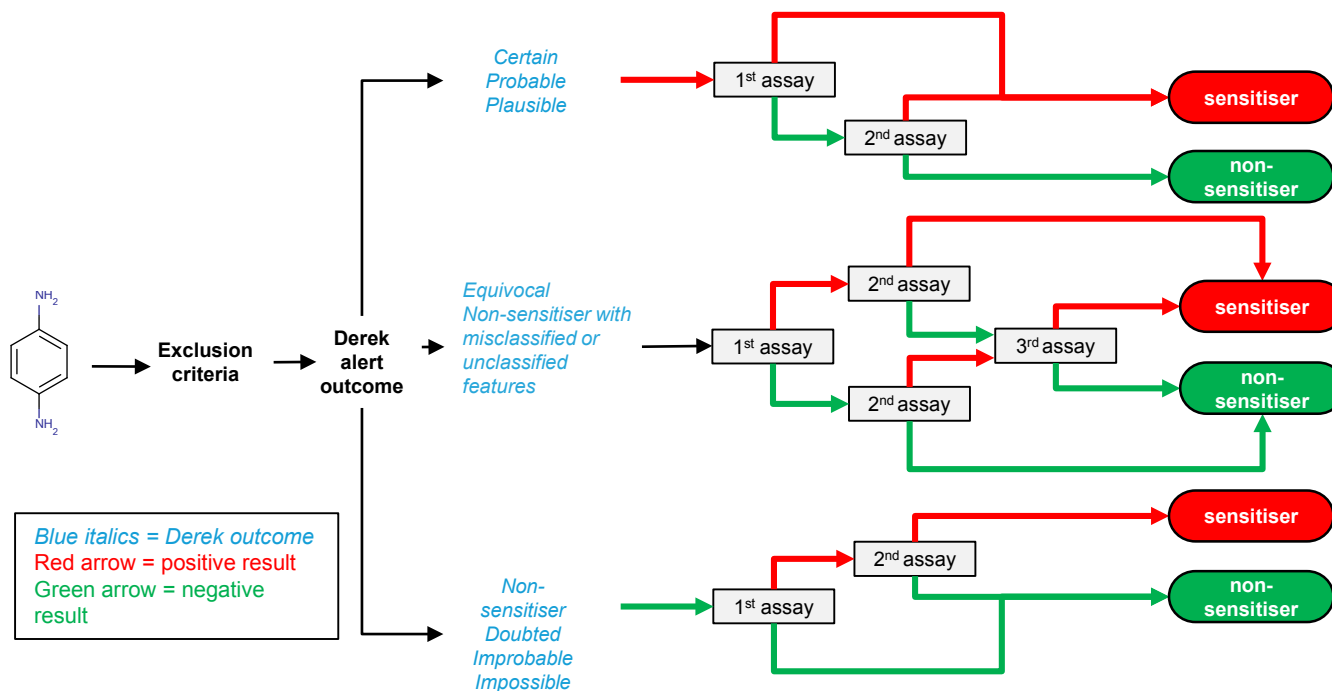
Prioritise *in chemico/in vitro* assays using exclusion criteria

Use Derek outcome to determine decision tree branch

Run *in chemico/in vitro* assays in order of AOP (MIE → KE2 → KE3) unless de-prioritised by exclusion criteria

Hazard prediction using '2 out of 3' approach

Potency prediction using k-nearest neighbours model



Potency prediction model

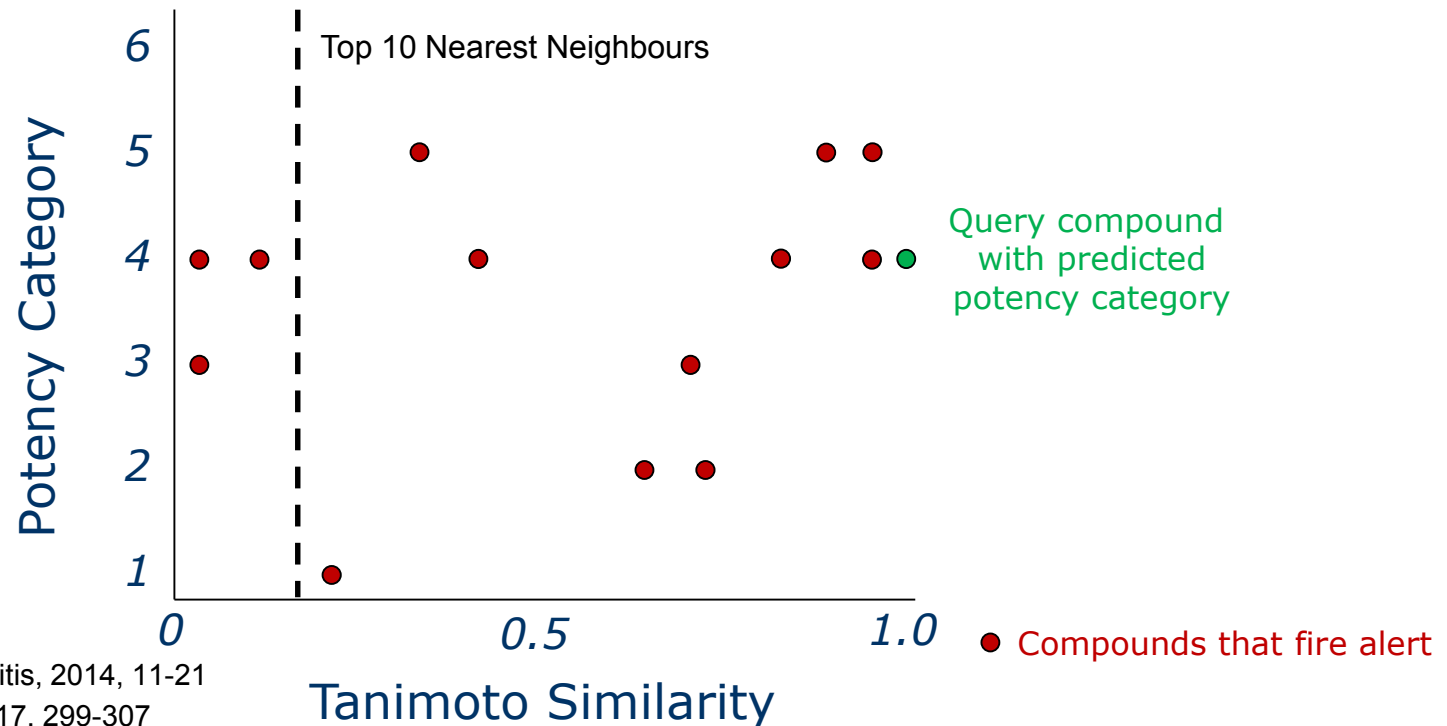
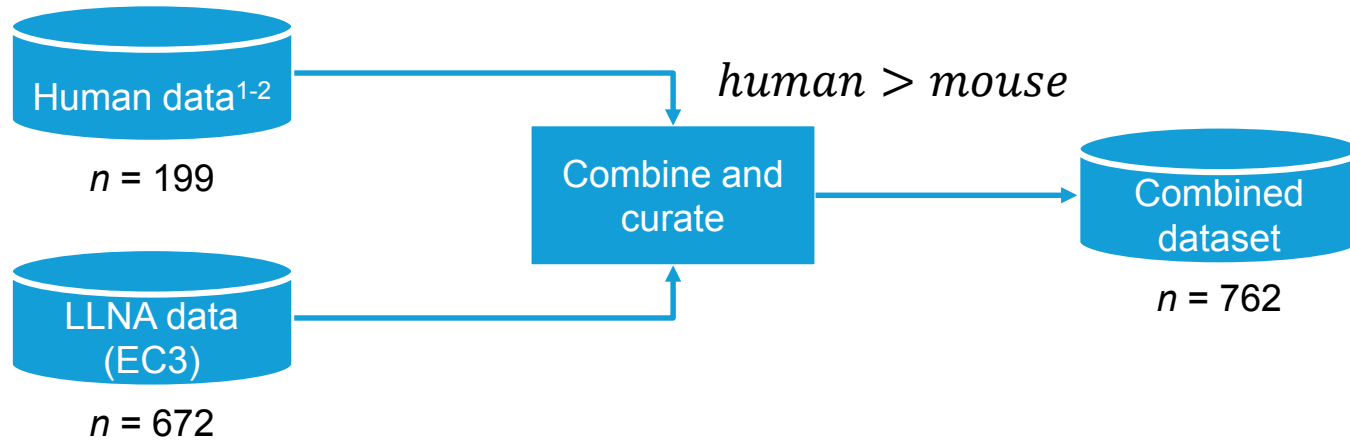
Potency category	Potency category name	GHS category	Equivalent EC3 value (%) ³
1	extreme	1A	< 0.2
2	strong	1A	< 2
3	moderate	1B	2 – 20
4	weak	1B	> 20 – 80
5	very weak/non-sensitiser	2	> 80
6	non-sensitiser	2	negative

1. Basketter et al., Dermatitis, 2014, 11-21

2. Api et al, Dermatitis, 2017, 299-307

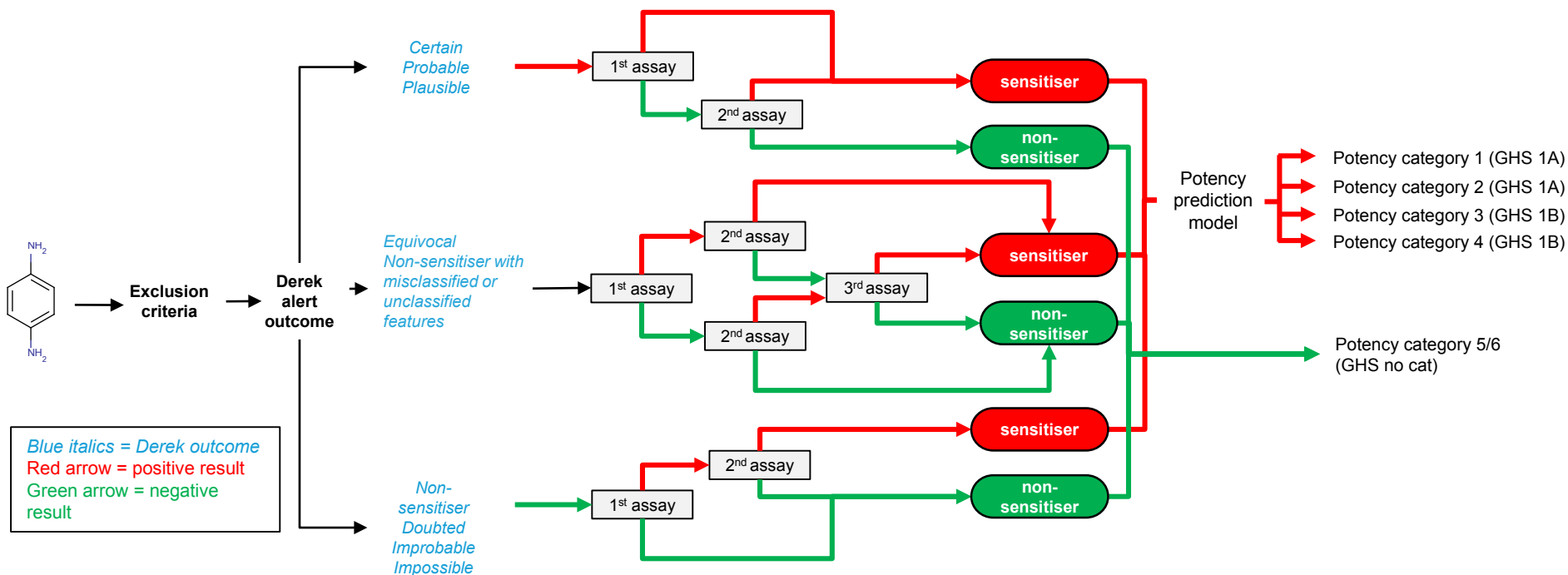
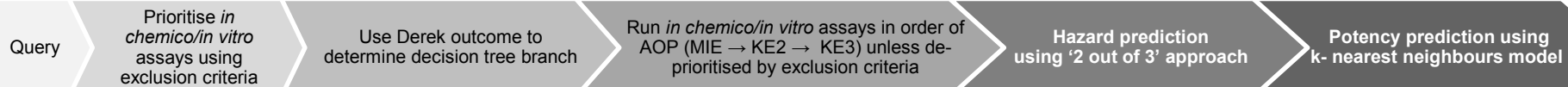
3. Basketter, 2016, Altern. Lab. Anim., 431–436

Potency prediction model



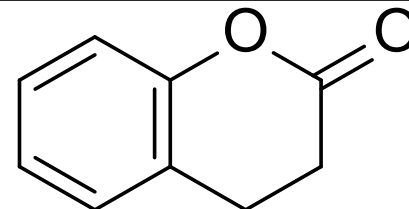
1. Basketter et al., *Dermatitis*, 2014, 11-21
2. Api et al, *Dermatitis*, 2017, 299-307
3. Basketter, 2016, *Altern. Lab. Anim.*, 431-436

Potency prediction



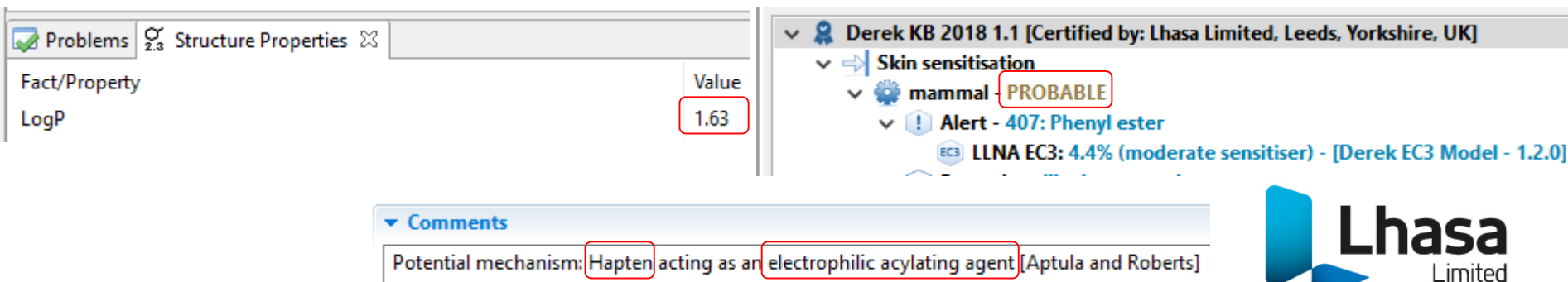
Example 1 - 3,4-dihydrocoumarin

Sensitiser in LLNA (EC3 = 5.6%)
Sensitiser in humans
Human potency category 3 / GHS 1B



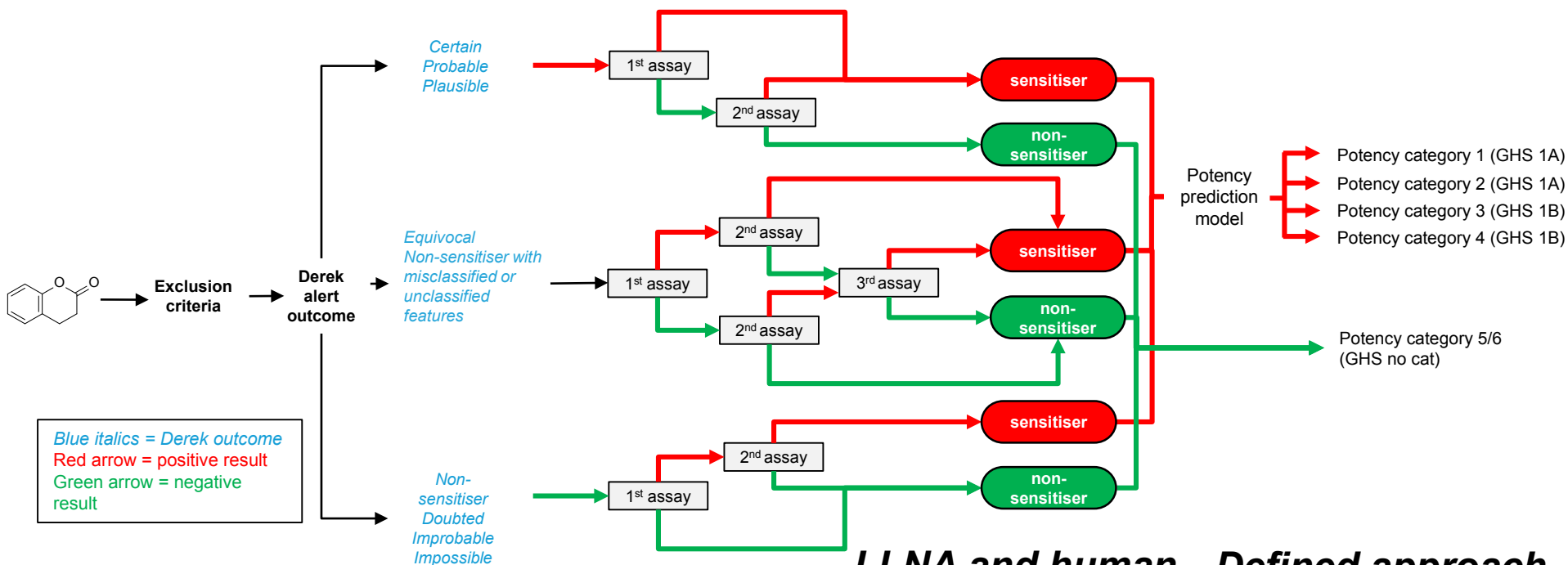
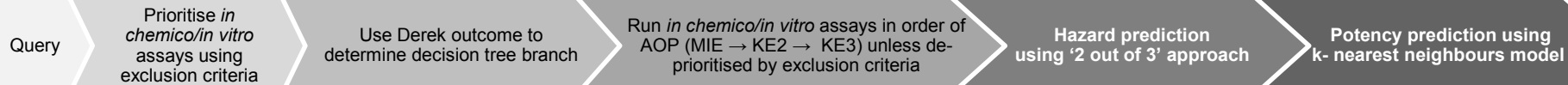
Exclusion criteria	Chemical property	Information source(s) excluded
Metabolism	Hapten	none
Lipophilicity	1.63	none
Lysine reactivity	Yes	KE2
Derek reasoning level	Probable	none
Derek negative prediction	n/a	-

Information from Derek



The screenshot displays the Derek software interface. On the left, the 'Structure Properties' tab is active, showing a table with 'LogP' and a value of '1.63'. On the right, the 'Derek KB 2018 1.1' results are shown, including 'Skin sensitisation' with a 'PROBABLE' result for 'mammal' and an 'Alert - 407: Phenyl ester' with an 'LLNA EC3: 4.4% (moderate sensitiser)' prediction. At the bottom, the 'Comments' section states: 'Potential mechanism: Hapten acting as an electrophilic acylating agent [Aptula and Roberts]'.

Example 1 - 3,4-dihydrocoumarin



LLNA and human **Defined approach**

Sensitiser

Human potency
category 3
GHS 1B

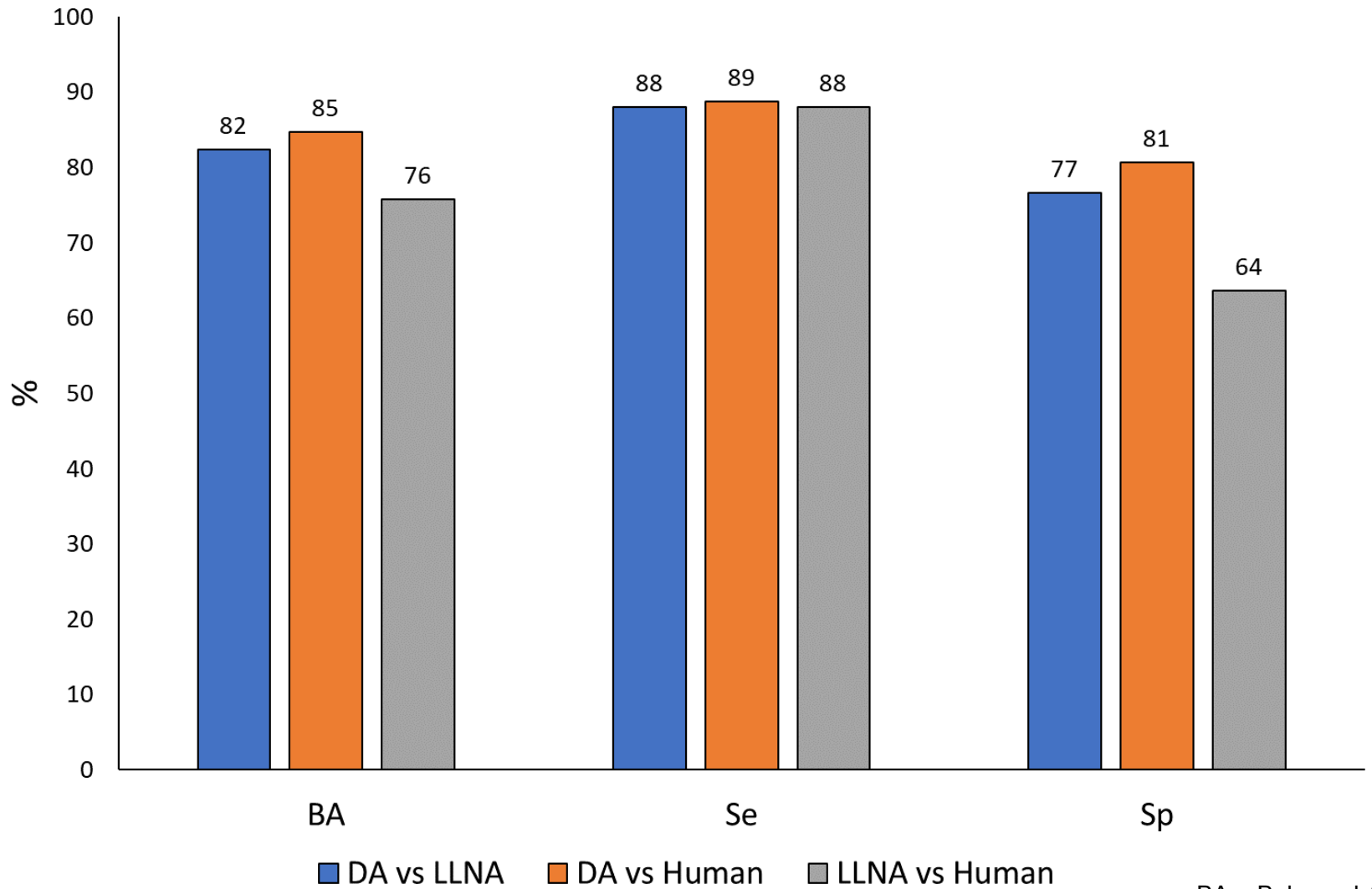
Sensitiser

Potency category 3
GHS 1B



AOP event	Information source	Outcome
AO	DX	probable
MIE/KE1	DPRA	positive
KE2	deprioritised	
KE3	h-CLAT/U-SENS™	positive

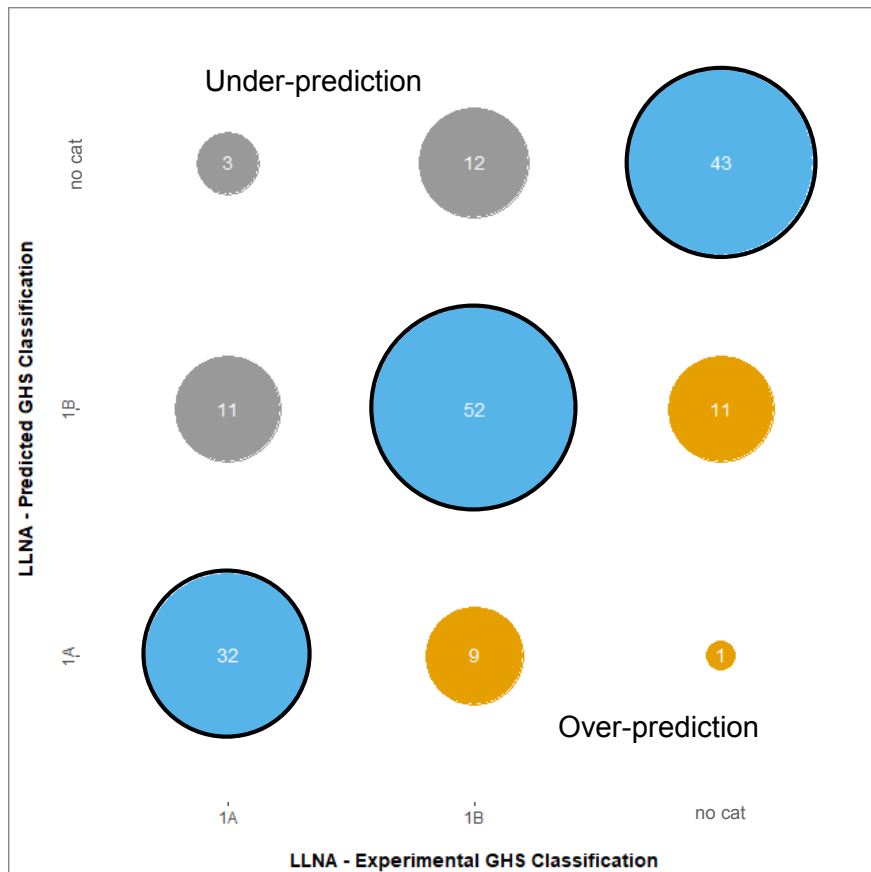
Results - Hazard



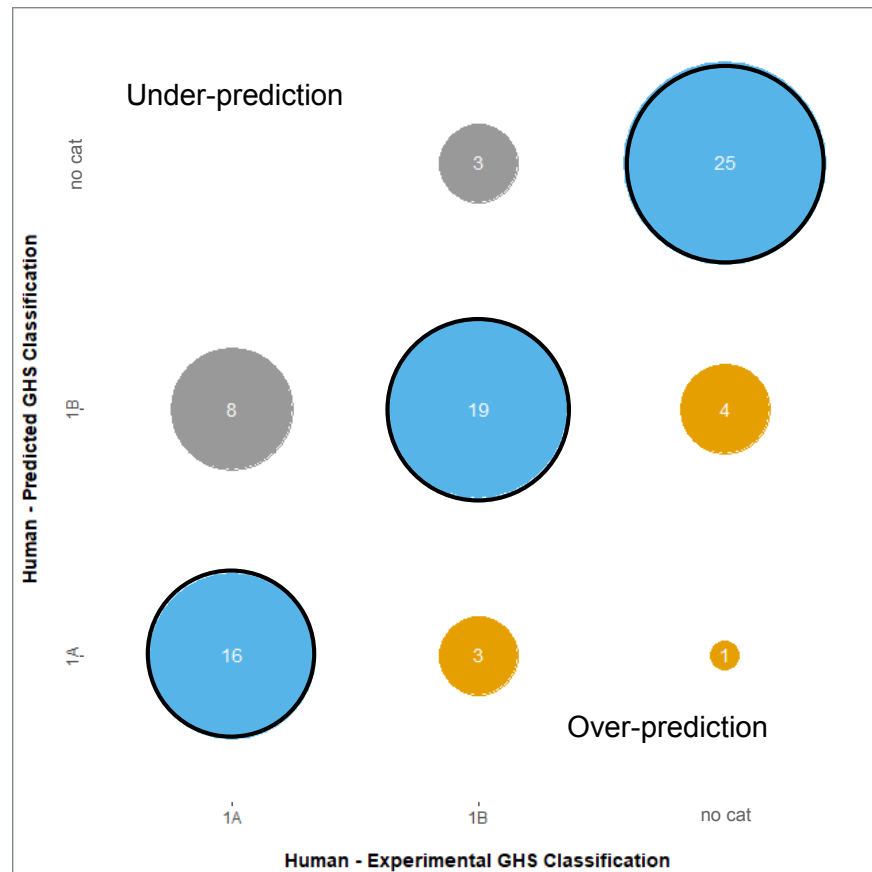
BA = Balanced Accuracy
Se = Sensitivity
Sp = Specificity

Results - Potency (GHS)

Defined approach prediction vs *in vivo* outcome



LLNA
 $n = 174$
 Acc = 73%



Human
 $n = 79$
 Acc = 76%

Conclusions

- A decision tree defined approach has been designed using exclusion criteria based on known limitations of *in chemico/in vitro* assays and Derek Nexus
- The defined approach correctly identifies:
 - 82% (LLNA) and 88% (human) as sensitisers/non-sensitisers (hazard)
 - The GHS classification for 73% (LLNA) and 76% (human) of chemicals in the evaluation dataset

Further work

- The mispredictions are being analysed and some upcoming improvements to Derek alerts will increase the accuracy of the DA
- Further work will be focussed on the validation of the defined approach using a test set of new *in chemico/in vitro* data
- Lhasa Limited are actively exploring and welcoming avenues and collaborators where this can be achieved

Acknowledgements

- Martyn Chilton
- Everyone at Lhasa Limited

