Webinar - Demonstration of a Defined Approach for Skin Sensitisation Web Application

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Overview

- Introduction to Lhasa's defined approach
- Demo of web-based application
- Questions

- Web app available at: https://skinsensda.lhasacloud.org
- All feedback very welcome

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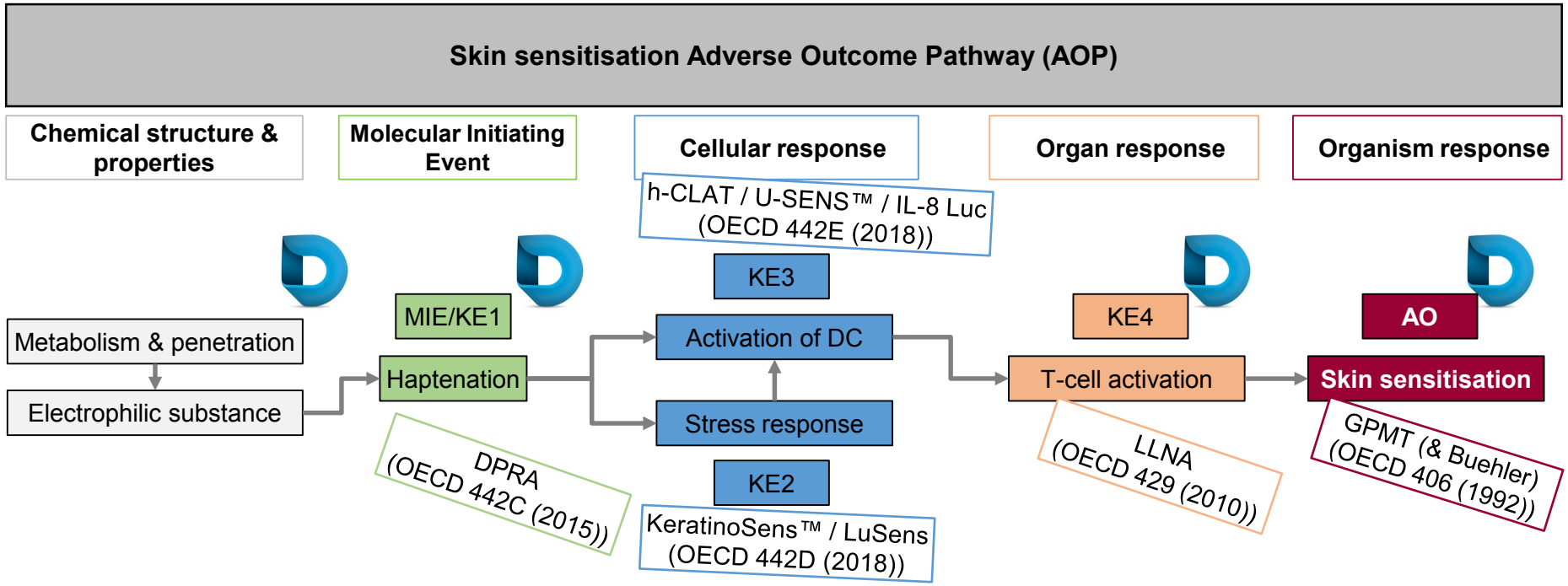
Skin sensitisation AOP

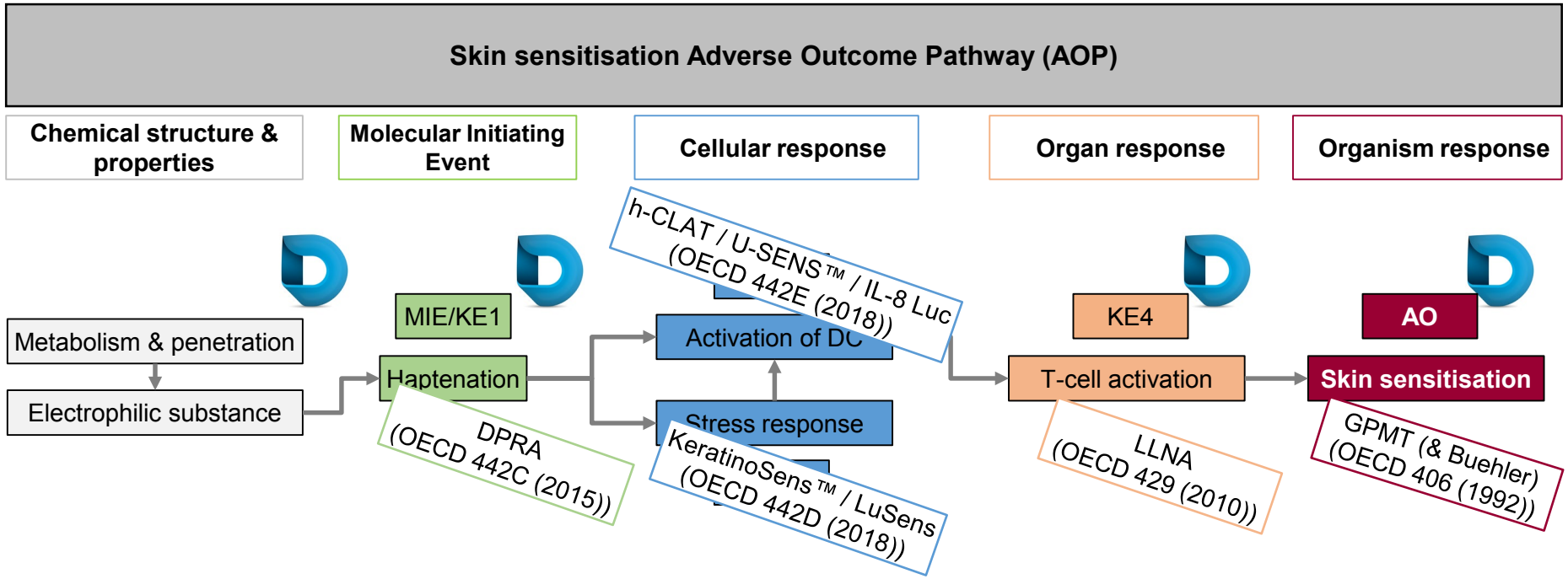


- *In vivo* assays no longer the preferred choice
- OECD-validated *in chemico/in vitro* assays now available
- A single assay cannot (yet) be used to replace *in vivo* tests

MIE = Molecular Initiating Event
KE = Key Event
DC = Dendritic Cells
AO = Adverse Outcome

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 AOP



- Instead multiple information sources must be combined in a **defined approach (DA)**
- Derek Nexus (Derek) covers many aspects of the AOP and would be a valuable complement to a defined approach

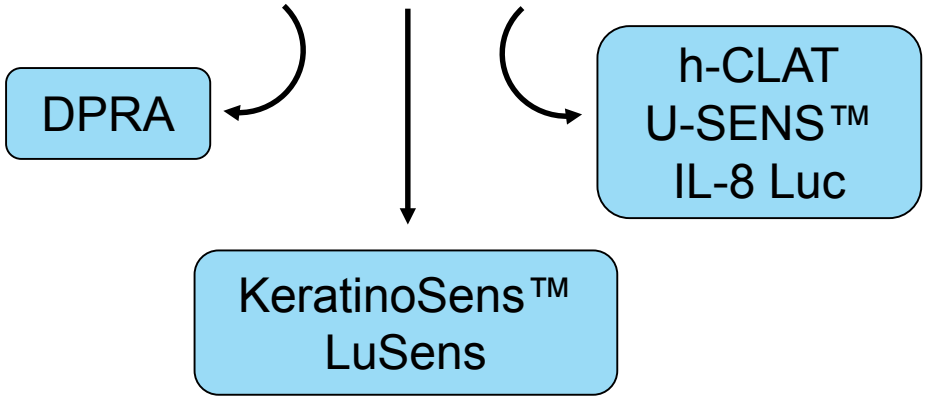
Figure adapted from OECD 2012, The Adverse Outcome Pathway for Skin Sensitisation Initiated by Covalent Binding to Proteins Part 1: Scientific Evidence, Series on Testing and Assessment, No. 168.

Lhasa's hypothesis

- Use a Key Event (KE) approach
  - Assays measuring the same KE will have similar limitations and applicability domains
- Apply **exclusion criteria** to chemicals:
  - Based on known assay limitations and confidence in Derek predictions
- Ensure the **most relevant** information source(s) are used for a given chemical (class)
  - By de-prioritising results from less applicable assays and/or predictions
- Use prioritised results until a concordant result is obtained - or a 2 out of 3 majority call

Exclusion criteria

Exclusion criteria	Derek	MIE	KE2	KE3	Comment

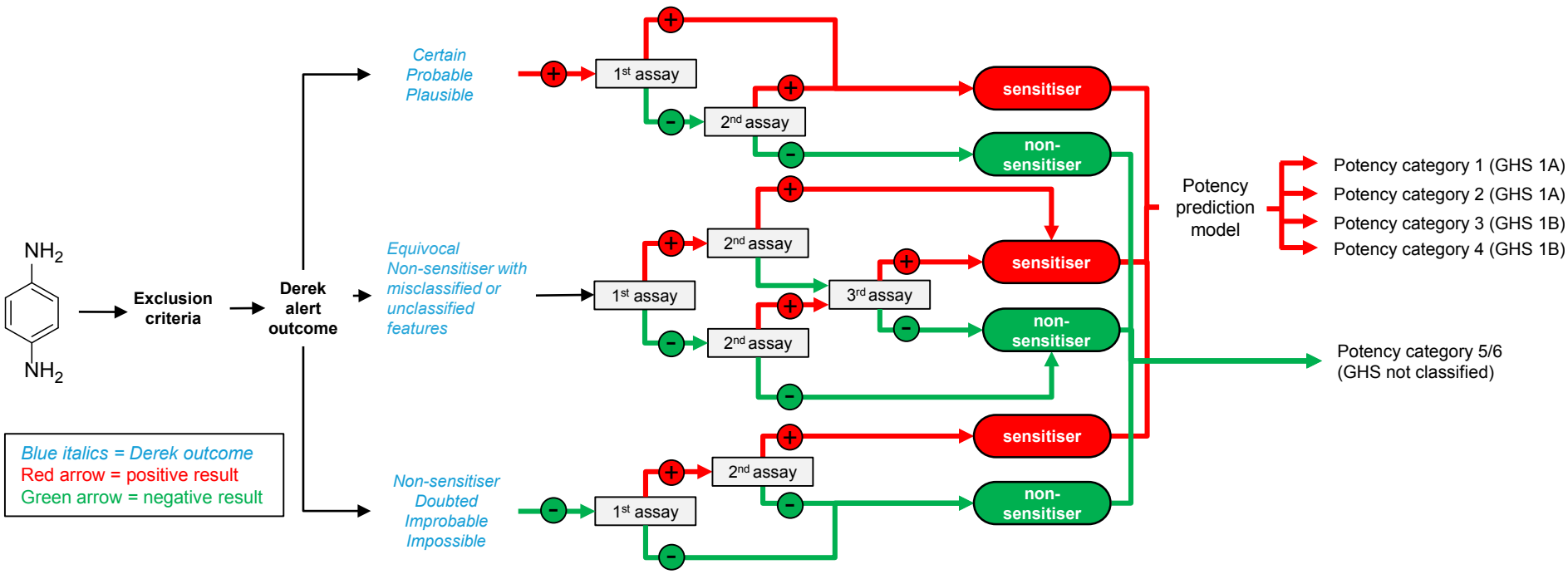


Exclusion criteria

Exclusion criteria		Derek	MIE	KE2	KE3	Comment
Metabolism	Prohapten	✓	✗	✓	✓	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			

Lhasa DA: 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**



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Lhasa DA: Potency prediction

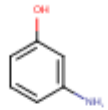
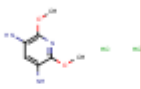
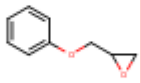
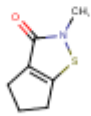
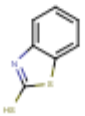
Human data[1-2]

n = 199

CAS No	Chemical Name	Human Binary Class	Human Potency Class
7487-94-7	Mercuric chloride	Positive	1
7778-50-9	Potassium dichromate	Positive	1
1330-20-7	Xylenes	Negative	6
7446-70-0	Aluminum chloride	Negative	6
13453-07-1	Gold trichloride	Positive	2
7787-56-6	Beryllium Sukfate	Positive	1
101-39-3	alpha-Methyl cinnamal	Positive	4

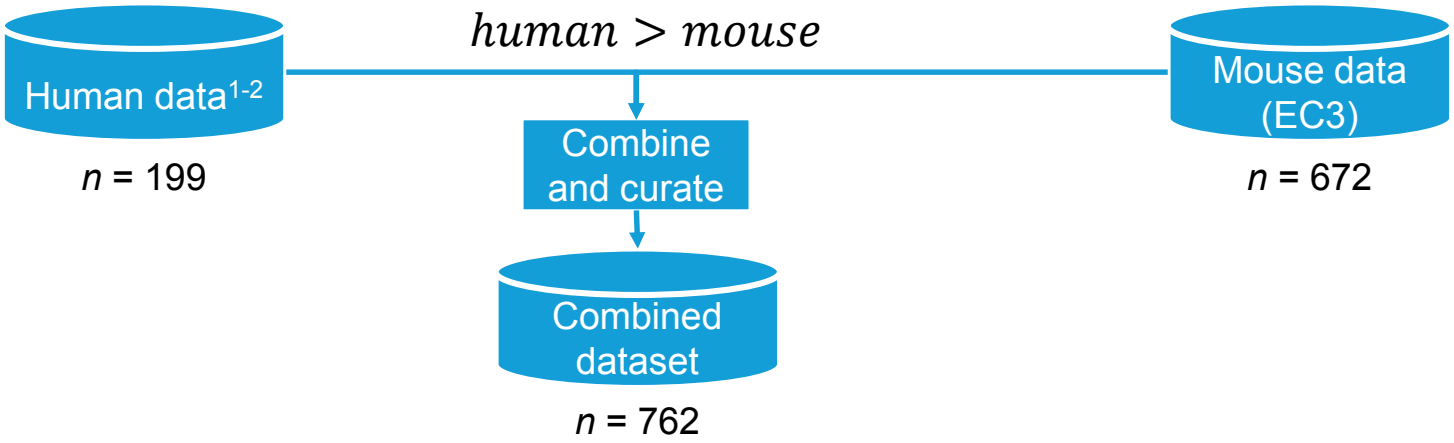
Mouse data (EC3)

n = 672

Lhasa ID	Mol Block	EC3
LL495		0.24
LL513		1.25
LL607		0.46
LL556		2
LL533		9.669

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

Lhasa DA: Potency prediction



Human potency category name	GHS Classification	Human potency category	Equivalent EC3 value (%)[3]
extreme	1A	1	< 0.2
strong	1A	2	0.2 – 2
moderate	1B	3	2 – 20
weak	1B	4	20 – 80
very weak/non-sensitiser	Not classified	5	> 80
non-sensitiser	Not classified	6	negative

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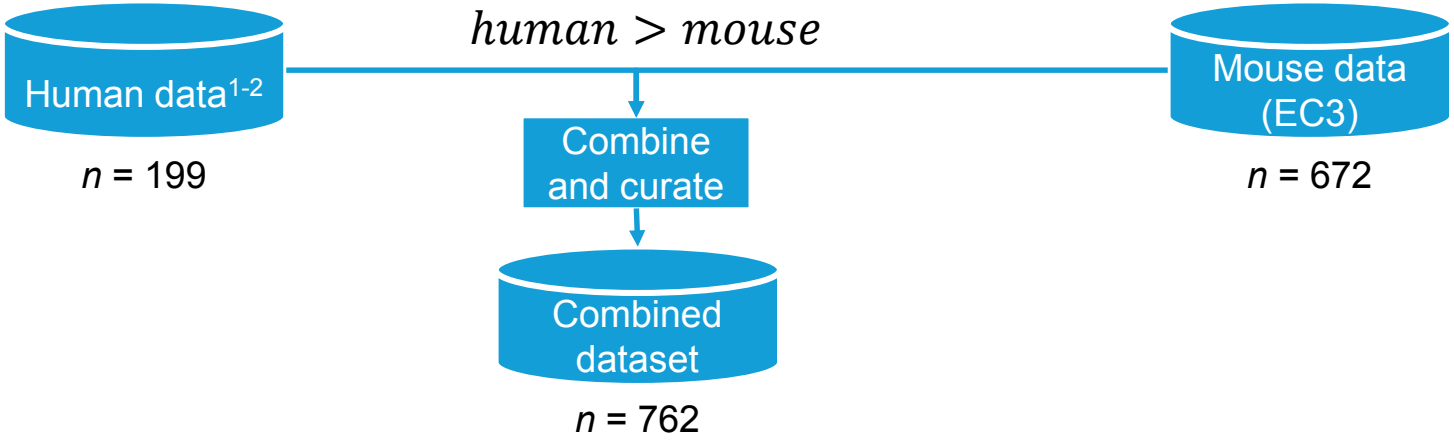
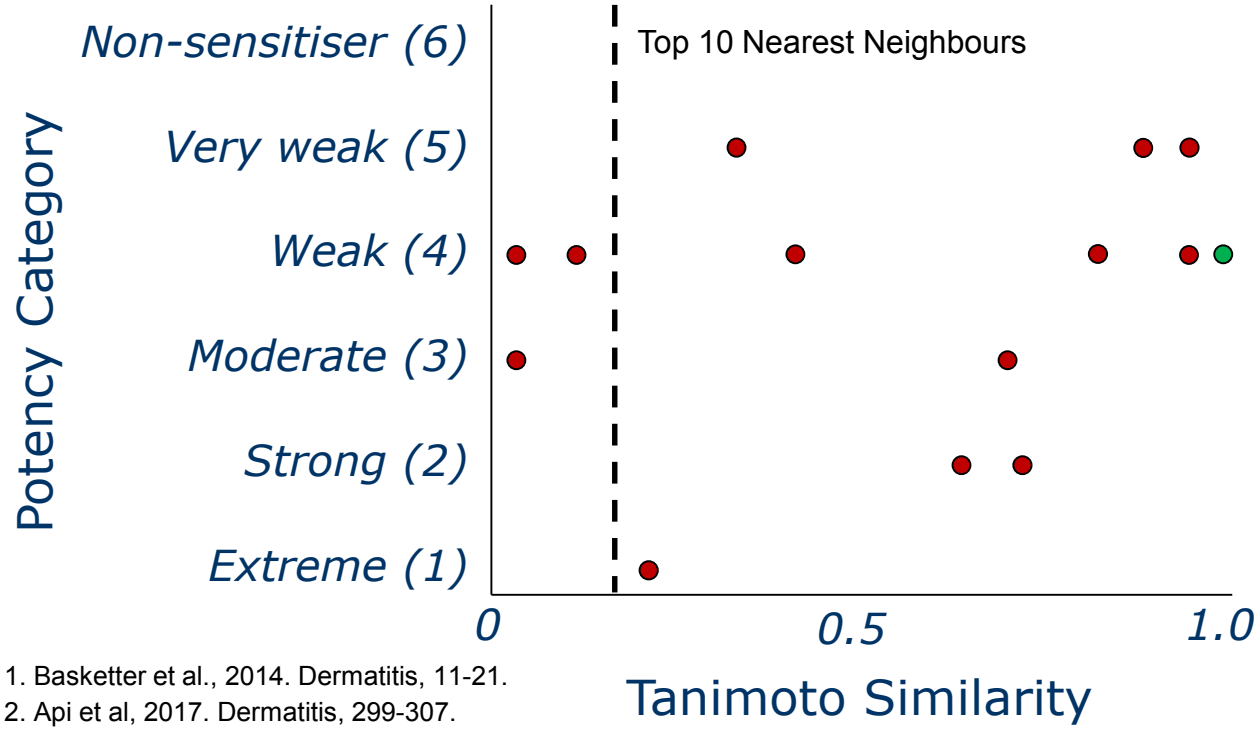
Lhasa DA: Potency prediction





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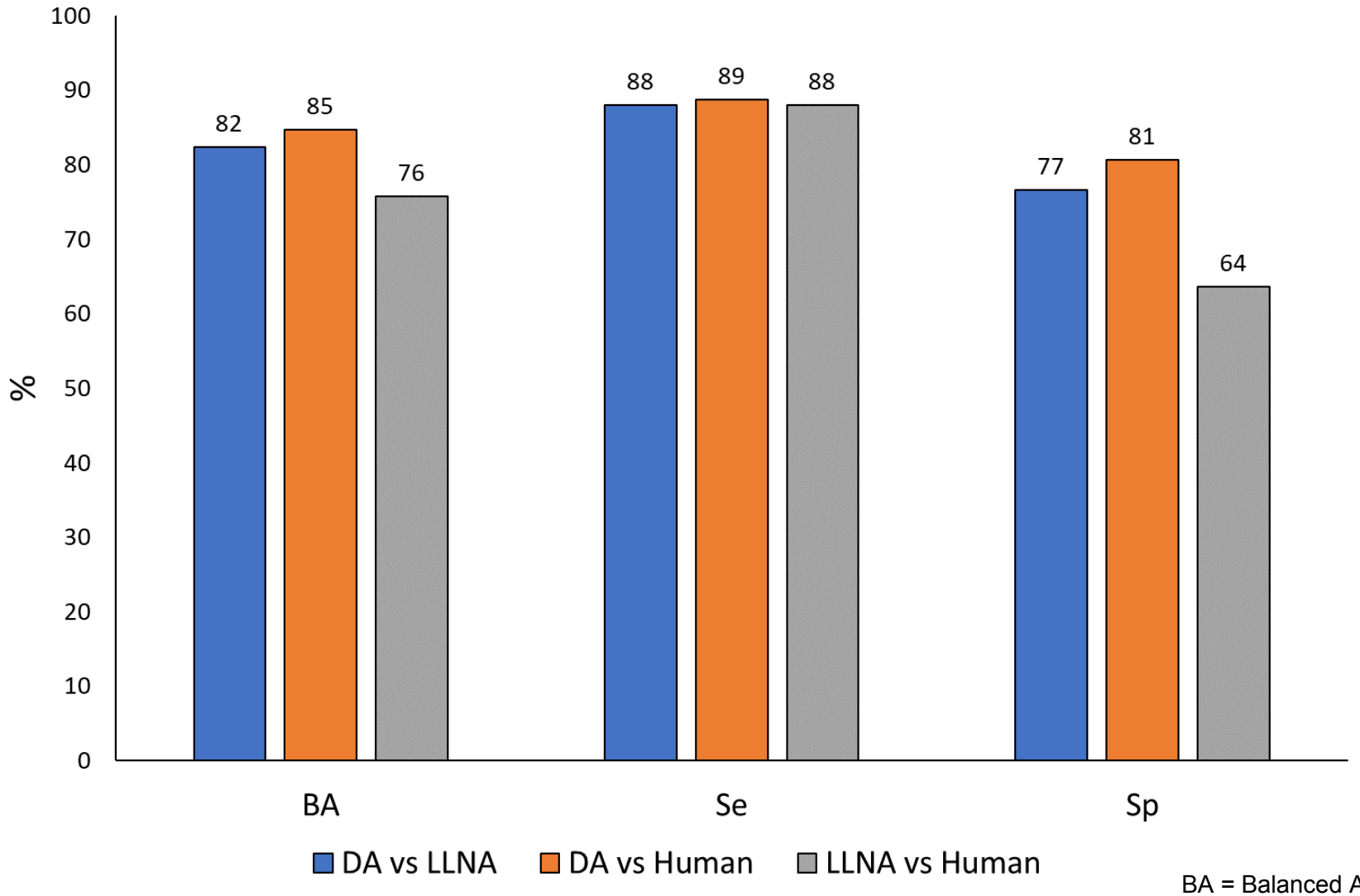
Results - Hazard

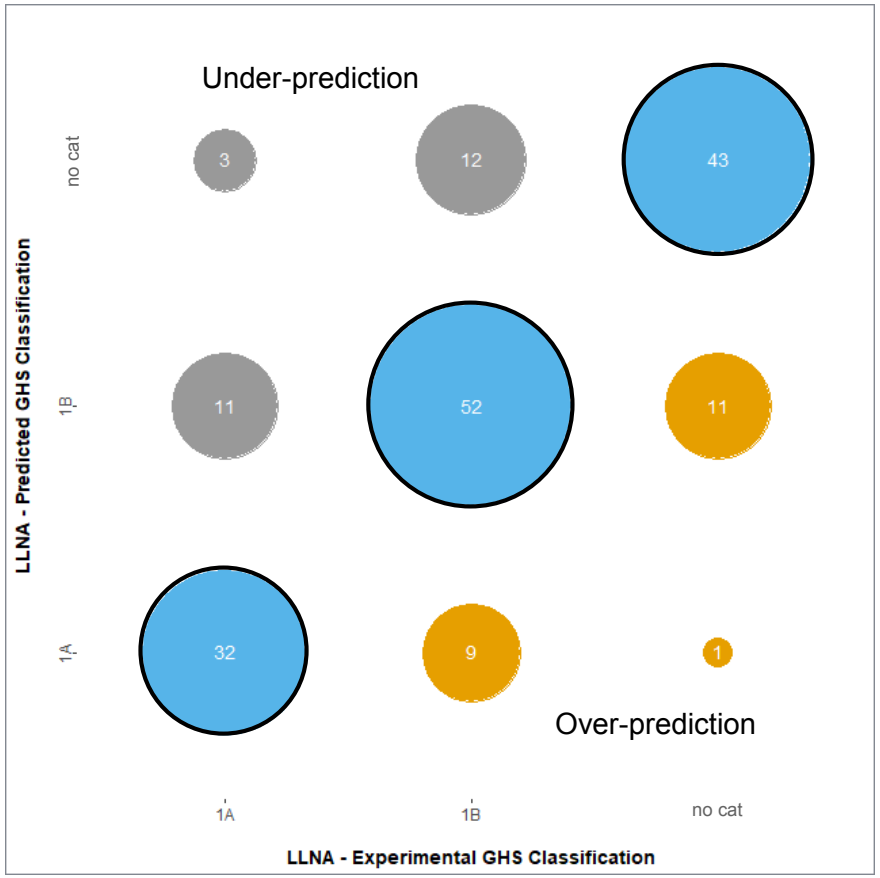


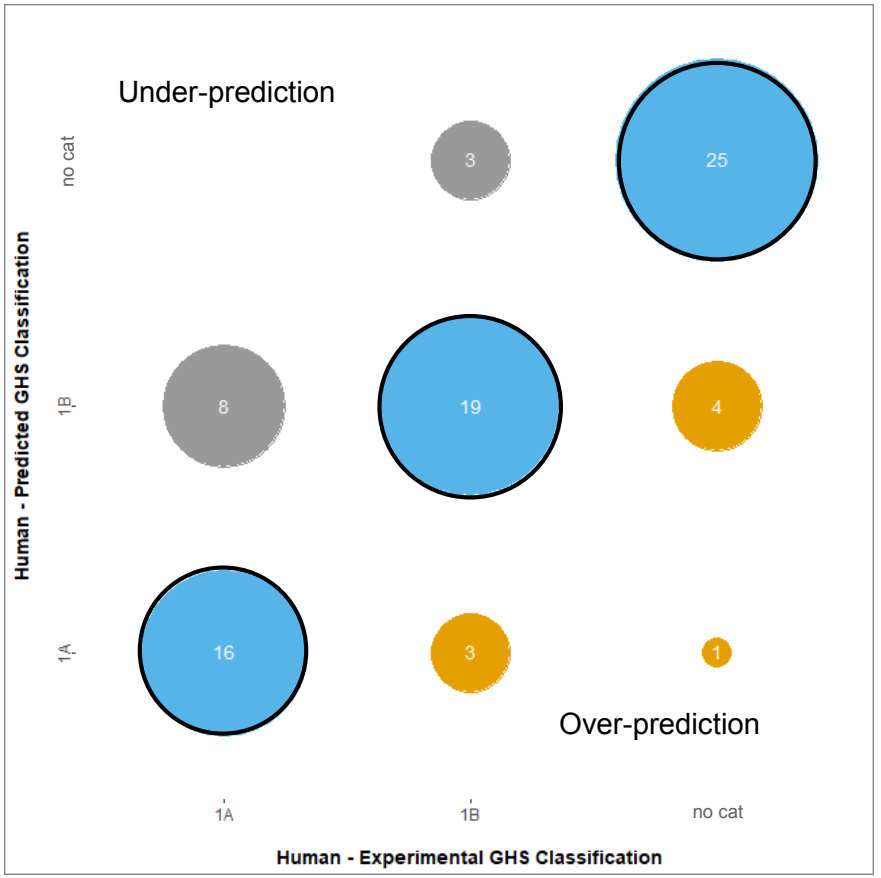
BA = Balanced Accuracy
Se = Sensitivity
Sp = Specificity

Based on a dataset of 210 chemicals from Urbisch et al.
Full analysis published in Macmillan & Chilton, Reg. Toxicol. Pharmacol. 2019, 101, 35-47.

Results - Potency (GHS Classification)

Defined approach prediction vs *in vivo* outcome





LLNA
n = 174
Acc = 73%

Human
n = 79
Acc = 76%

Full analysis published in Macmillan & Chilton, Reg. Toxicol. Pharmacol. 2019, 101, 35-47.

Demo of web app

Web app available at: https://skinsensda.lhasacloud.org

Conclusions

- Lhasa Limited have developed a web-based application for the previously published defined approach (DA) which incorporates *in silico* predictions with results from OECD-validated *in chemico / in vitro* assays
- The DA is currently being considered by the OECD for inclusion in the upcoming guidance on DAs
- Web app available at: https://skinsensda.lhasacloud.org
- All feedback very welcome

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Macmillan & Chilton, Reg. Toxicol. Pharmacol. 2019, 101, 35-47.

Acknowledgements

- Martyn Chilton
- Sam Webb
- Everyone at Lhasa Limited

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