A Defined Approach to Skin Sensitisation: Integrating Derek Nexus with *In Chemico/In Vitro* Assays Based on Exclusion Criteria

2nd Pan-American Conference For Alternative Methods
23rd August 2018

Dr Donna Macmillan

Principal Scientist

donna.macmillan@lhasalimited.org

Agenda

- Lhasa Limited
- Skin sensitisation
- Non-animal approaches
- Lhasa's defined approach
- Conclusions

Introduction to Lhasa Limited

- Established in 1983
- Not-for-profit & Educational Charity
- HQ located in Leeds, United Kingdom
- Facilitate collaborative data sharing projects in the chemistry-related industries
  - Shared Knowledge, Shared Progress
- Creators of knowledge base, statistical and database systems

Derek nexus

Zeneth

Meteor nexus

Sarah nexus

Mirabilis

Vitic

Lhasa Limited

What is skin sensitisation?

- Common occupational disease
- Not life-threatening but lifelong
- M nt ec isting, leg e redict sk ti



EU REACH Cosmetics Regulation

Korea REACH

China REACH

USA – Amended TSCA

Turkey KKDIK

Brazil cosmetics ban?

How is it assessed *in vivo*?

- Traditionally assessed *in vivo* using mice or guinea pigs

OECD/OCDE

429

Adopted:
22 July 2010

OE

406

Adopted:
17.07.92

OECD GUIDELINE FOR TESTING OF CHEMICALS

Adopted by the Council on 17th July 1992

Skin Sensitisation

- Interest in non-animal approaches has been increasing

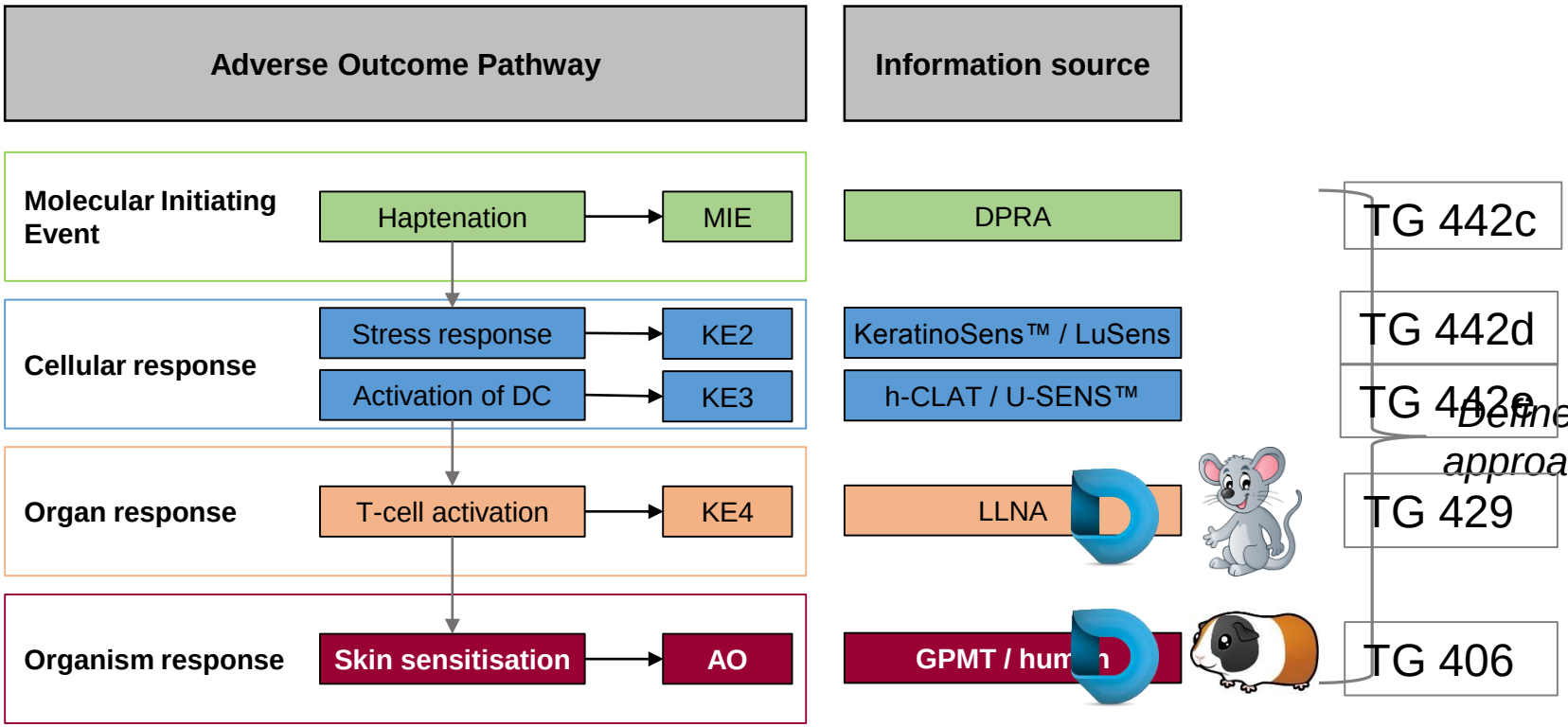
Adverse Outcome Pathway

Adverse Outcome Pathway			Information source	
Molecular Initiating Event	Haptenation	MIE		
Cellular response	Stress response	KE2		
	Activation of DC	KE3		
Organ response	T-cell activation	KE4	LLNA	TG 429
Organism response	**Skin sensitisation**	**AO**	**GPMT / human**	TG 406

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 Limited

Adverse Outcome Pathway



- *In chemico/in vitro* assays can't be used in isolation
- *In silico* predictions may provide valuable information

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 Limited

Lhasa's defined approach

MIE	KE2	KE3	AO
DPRA	KeratinoSens™ LuSens	h-CLAT U-SENS™	

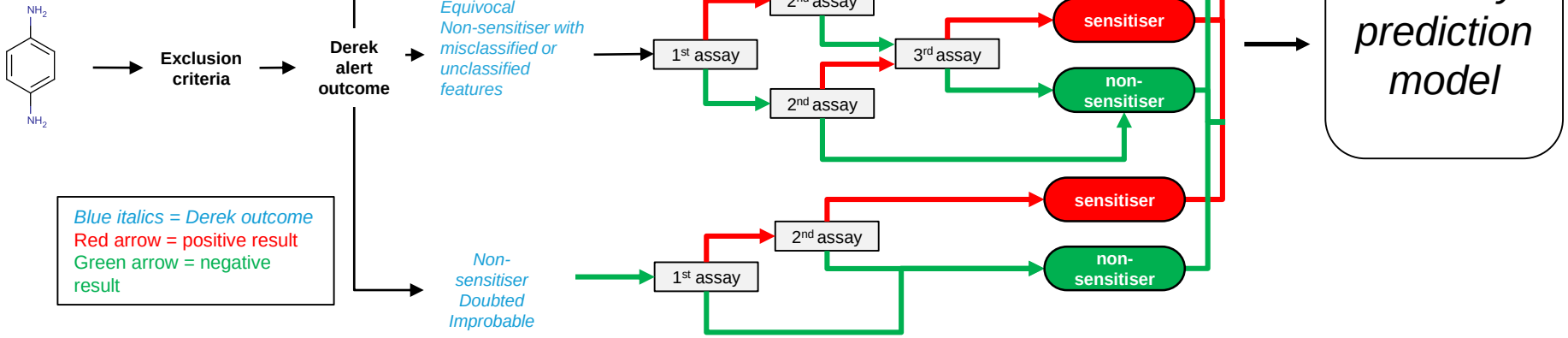
- Our hypothesis:
  - Use Derek information alongside assay data (grouped into key events in the AOP)
  - Apply **exclusion criteria** to take into account applicability domain
  - Ensure the most relevant information source(s) are used for specific chemicals

Summary of 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

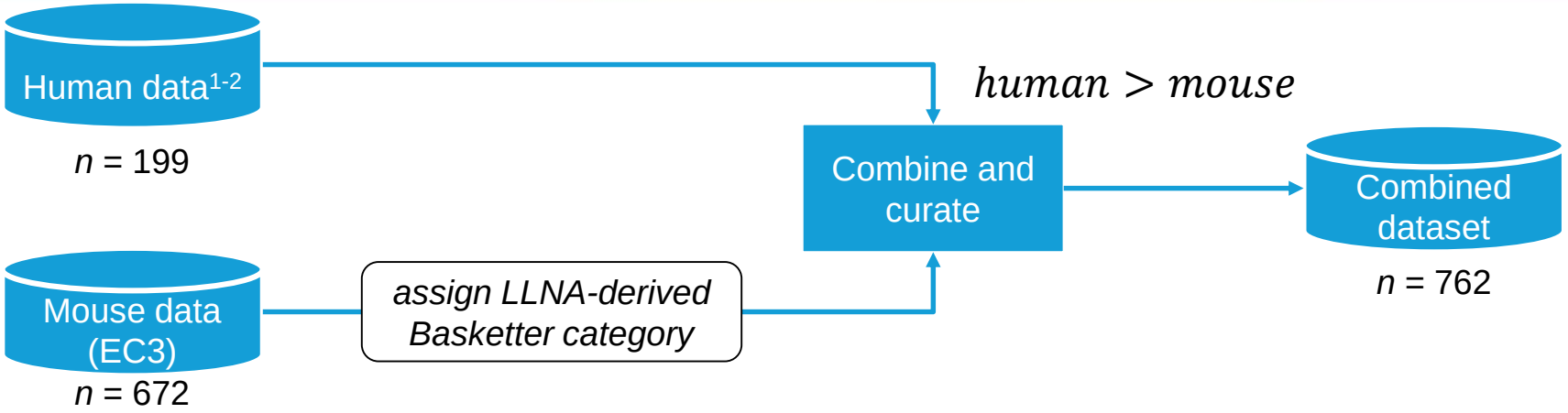
Hazard prediction

Chemical of interest → 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**



Lhasa Limited

Potency prediction model



6 | Top 10 Nearest Neighbours

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

0 0.5 1.0

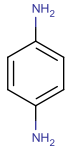
Tanimoto Similarity

● Compounds that fire alert

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

Chemical of interest → 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**



Exclusion criteria

Derek alert outcome

Certain
Probable
Plausible

1st assay → 2nd assay → **sensitiser** / **non-sensitiser**

Equivocal
Non-sensitiser with misclassified or unclassified features

1st assay → 2nd assay → 3rd assay → **sensitiser** / **non-sensitiser**

Non-sensitiser
Doubted
Improbable

1st assay → 2nd assay → **sensitiser** / **non-sensitiser**

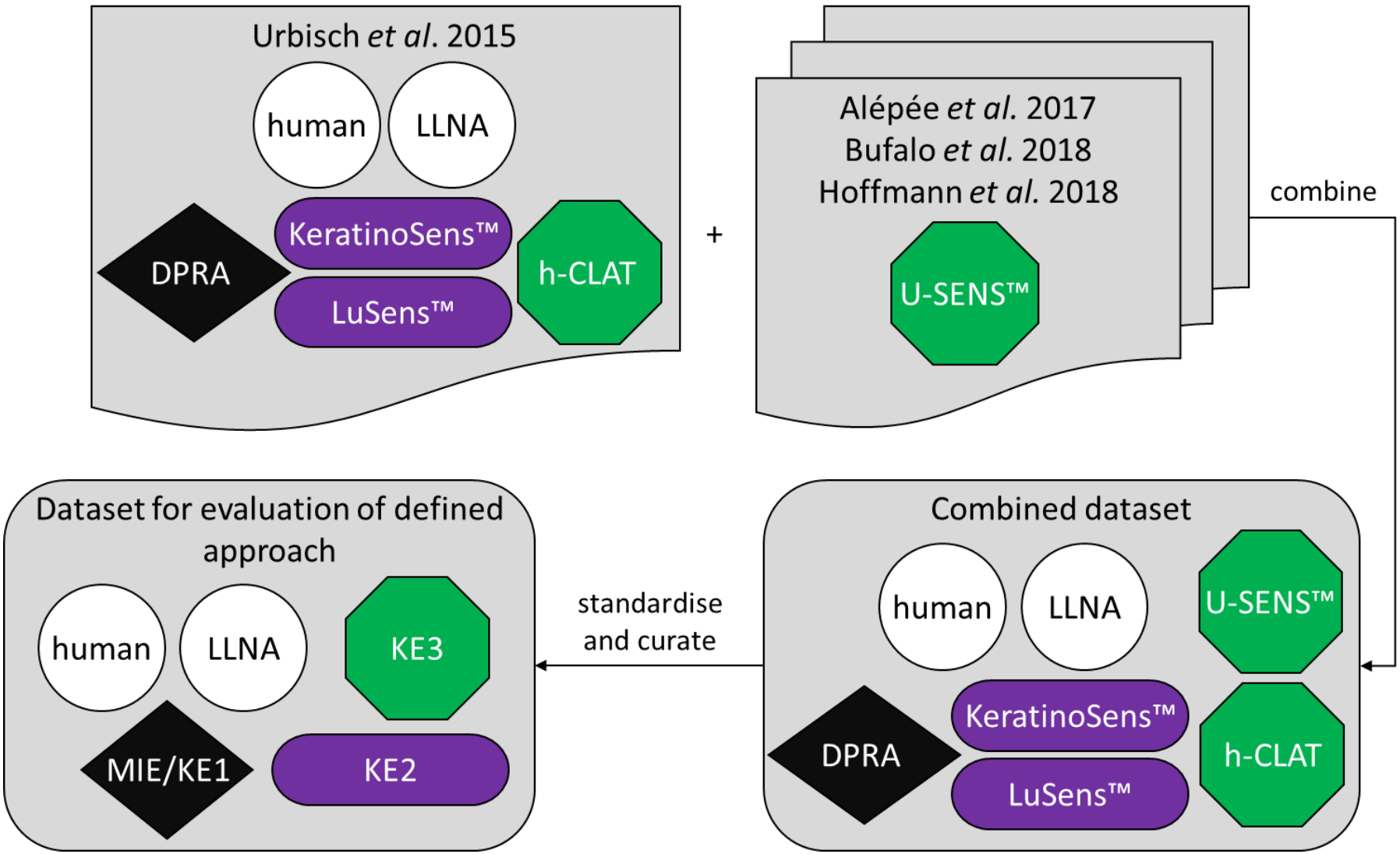
Potency prediction model

- Basketter 1 (GHS 1A)
- Basketter 2 (GHS 1A)
- Basketter 3 (GHS 1B)
- Basketter 4 (GHS 1B)
- Basketter 5/6 (GHS no category)

Blue italics = Derek outcome
Red arrow = positive result
Green arrow = negative result

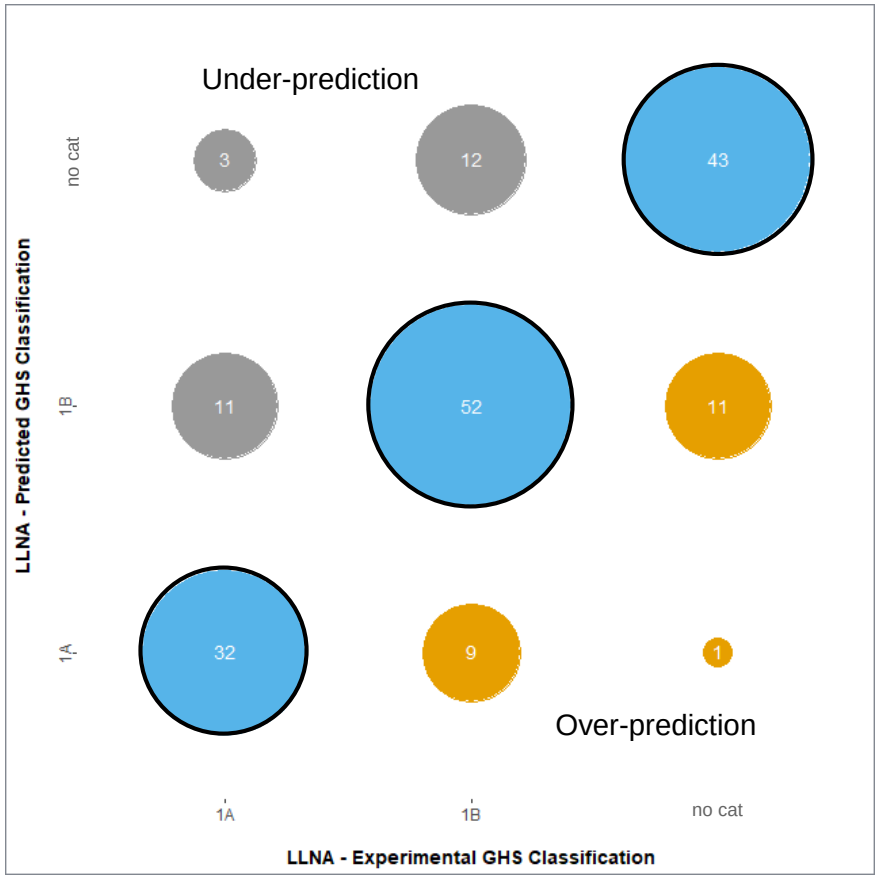
Lhasa Limited

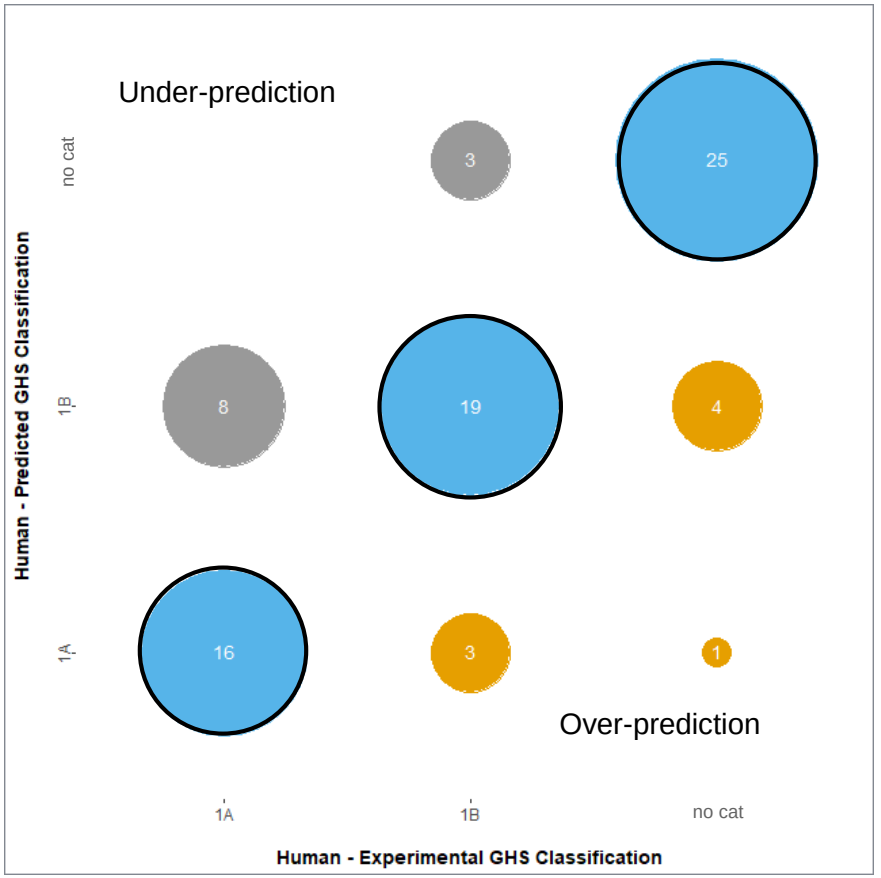
Dataset compilation



Results

Defined approach prediction vs *in vivo* outcome



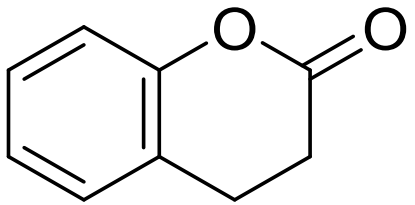


LLNA
n = 174
Acc = 73%

Human
n = 79
Acc = 76%

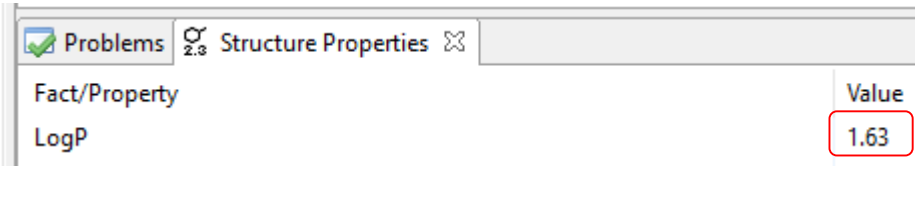
Example 1 - **3,4-dihydrocoumarin**

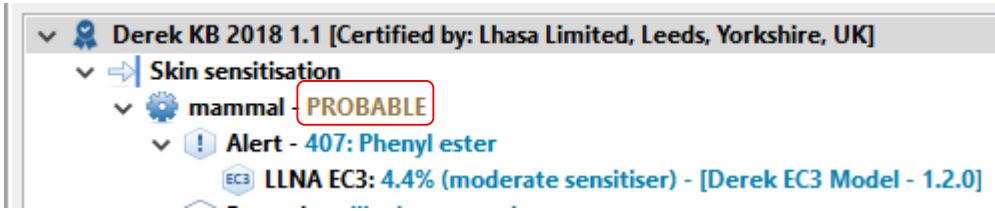
Sensitiser in LLNA (EC3 = 5.6%)
Sensitiser in humans[1]
Basketter category 3 / GHS 1B

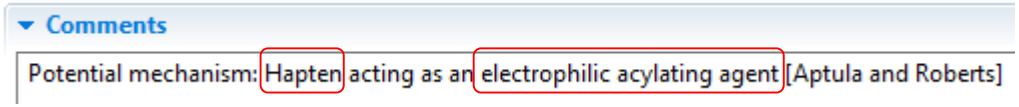


Exclusion criteria	Chemical property	Information source(s) excluded

Information from Derek



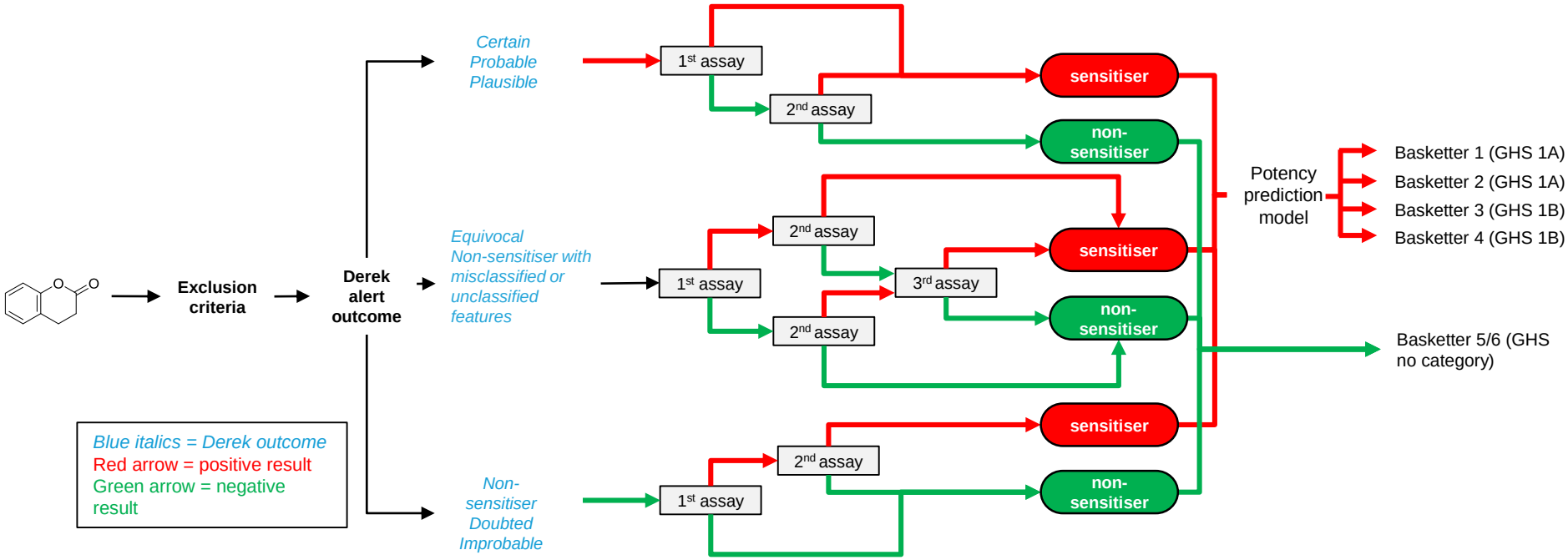




1. Urbisch *et al*., Regulatory Pharmacol. Toxicol., 2015, 337-51

Example 1 - **3,4-dihydrocoumarin**

Chemical of interest → 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**



AOP element	Information source	Outcome
KE1	DX	probable
KE2	DPRA	positive
KE3	h-CLAT/U-SENS™	positive

LLNA and human Sensitiser Basketter category 3 GHS 1B

Defined approach Sensitiser Basketter category 3 GHS 1B

deprioritised

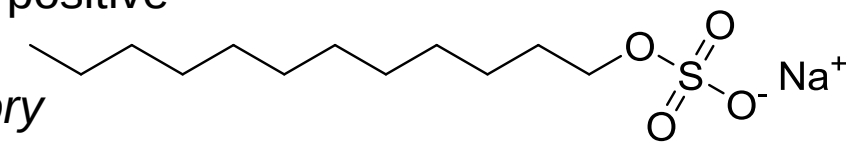
Lhasa Limited

Example 2 – **sodium lauryl sulfate**

Sensitiser in LLNA (no EC3) – known false positive

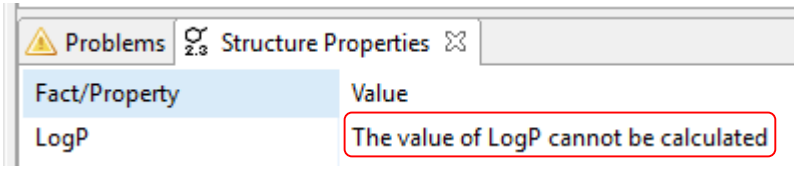
Non-sensitiser in humans[1]

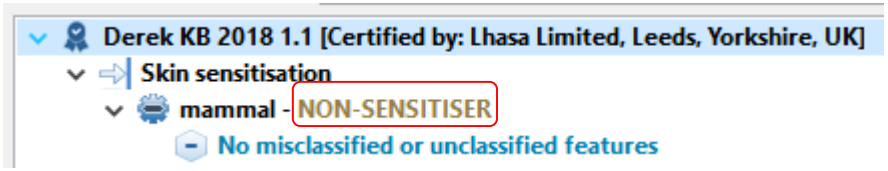
Basketter category 6 / GHS no category



Exclusion criteria	Chemical property	Information source(s) excluded

Information from Derek

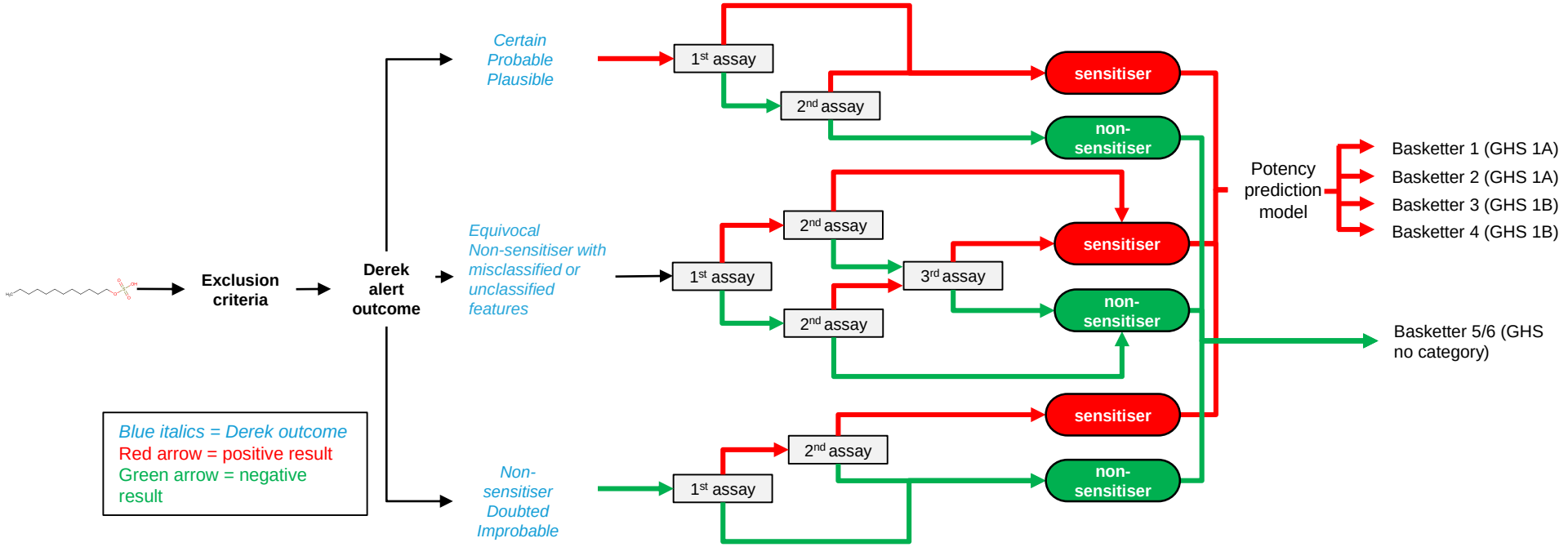




1. Urbisch *et al*., Regulatory Pharmacol. Toxicol., 2015, 337-51

Example 2 – **sodium lauryl sulfate**

Chemical of interest → 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**



Key event	Assay / model	Outcome
MIE	DX	Non-sensitiser
KE2	DPRA	no data
KE2	KeratinoSens™ / LuSens	negative
KE3	h-CLAT / U-SENS™	**no data**

Human Defined approach

Non-sensitiser **Non-sensitiser**

Basketter category 6 *Basketter category 5/6*

GHS no category *GHS no category*

Lhasa Limited

Conclusions

- A simple, transparent, 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 predicts:
  - ***DA vs LLNA***
    - The Basketter potency category for 59% and the GHS classification for 73%
  - ***DA vs Human***
    - The Basketter potency category for 68% and the GHS classification for 76% of chemicals

Lhasa Limited