



The application of *in silico* models to support decision making in toxicology

Dr Chris Barber, CEO

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March 2020



on behalf of Dr Richard Williams

Our ambition

to eliminate animal studies without compromising safety

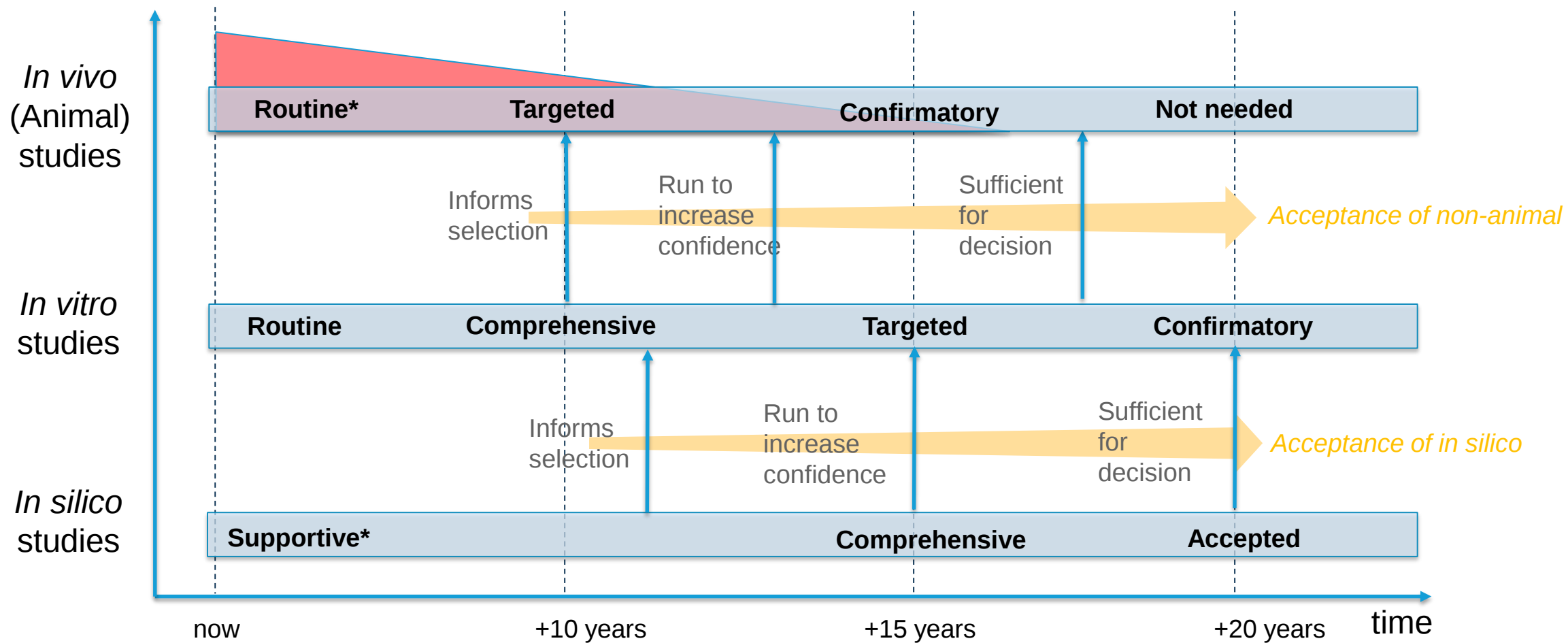
A guide to how *in silico* can play a key part



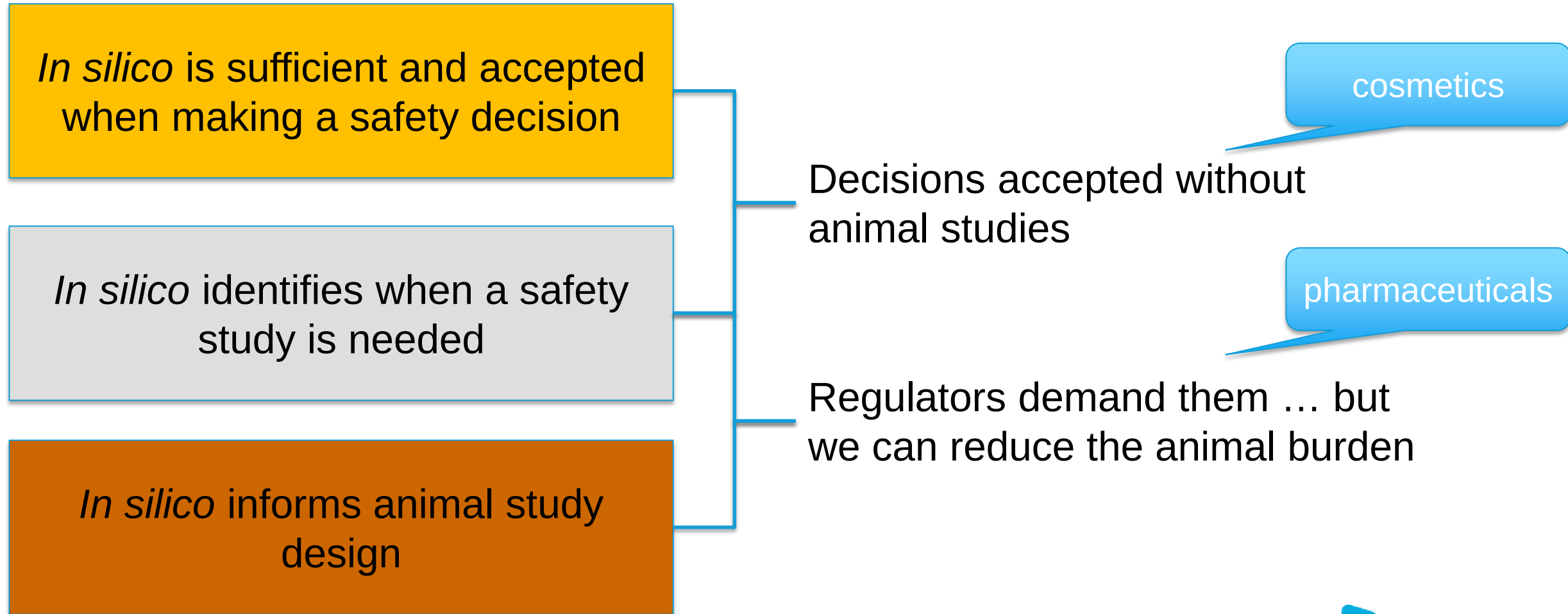
Agenda

- A view of the future of safety toxicology
- Developing *in silico* methods to support safety decisions

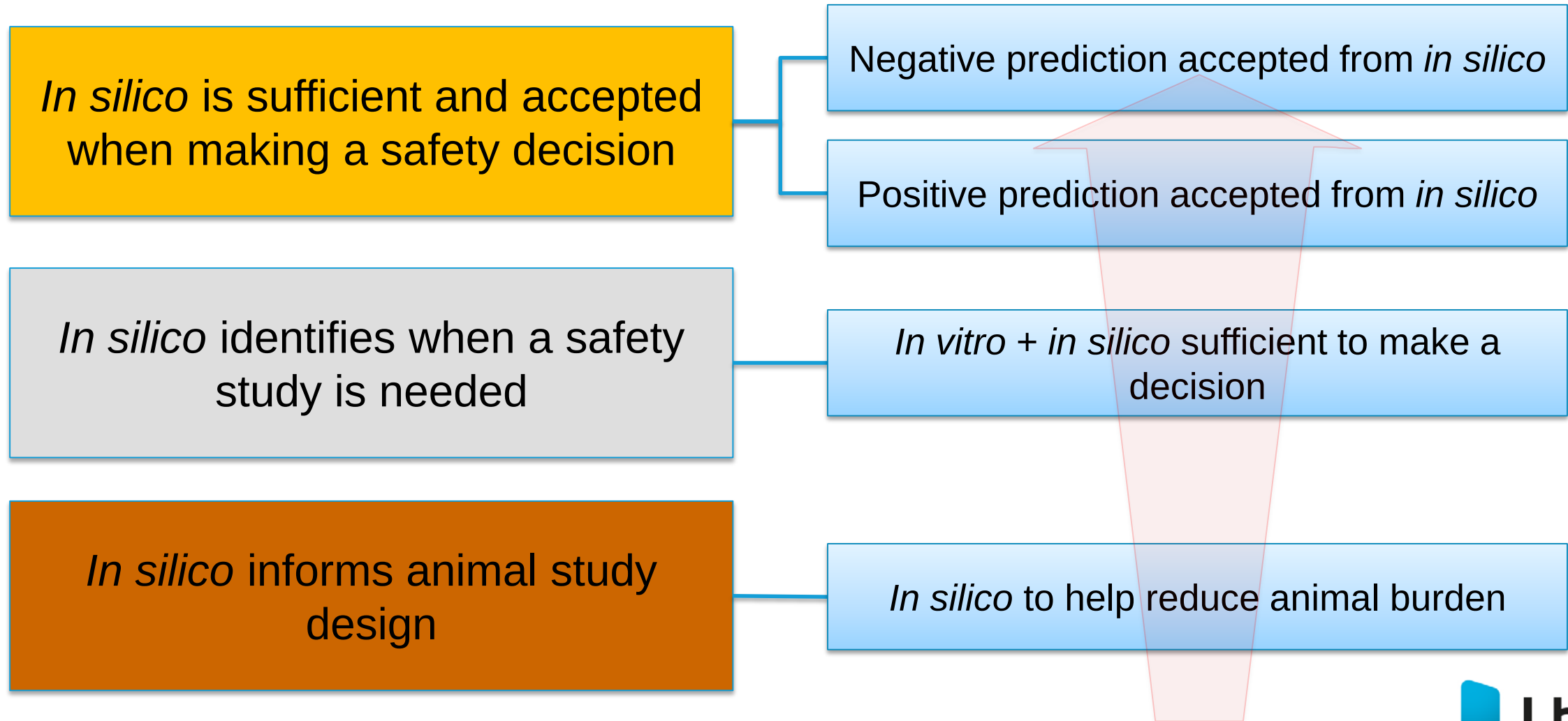
A view of the future of safety toxicology



Opportunities for *in silico* to support safety decisions



Opportunities for *in silico* to support safety decisions



In silico can help reduce animal testing

- Better study design
 - Single species submissions
 - Use of historical data to select appropriate species, reduce study size...
 - Use of virtual control animals

ALTEX – Concept Article (Food for Thought)

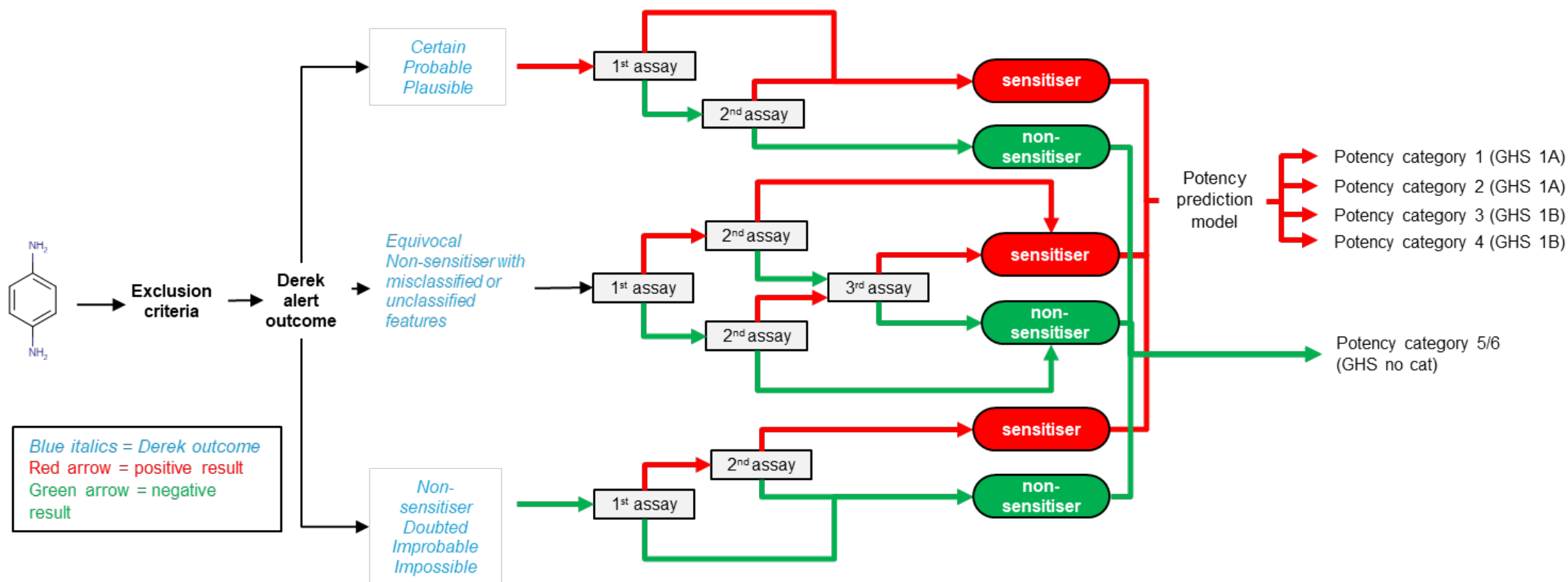
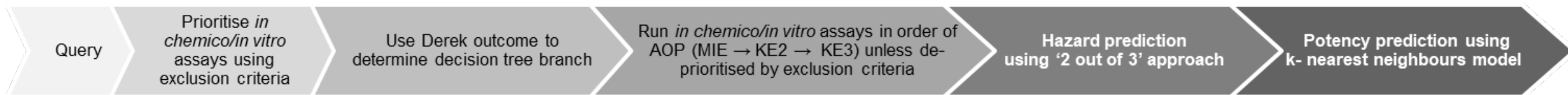
Introducing the Concept of Virtual Control Groups into Preclinical Toxicology Testing

Thomas Steger-Hartmann¹, Annika Kreuchwig¹, Lea Vaas¹, Jörg Wichard¹, Frank Bringezu², Alexander Amberg³, Wolfgang Muster⁴, Francois Pognan⁵, Chris Barber⁶

submitted



In vitro + *in silico* = sufficient to make a decision



P601 Updated Dermal Sensitization Thresholds Derived Using an *In Silico* Expert System and an Expanded LLNA Dataset

Donna Macmillan 18th March, pm, Exhibit Hall

Positive prediction accepted from *in silico*

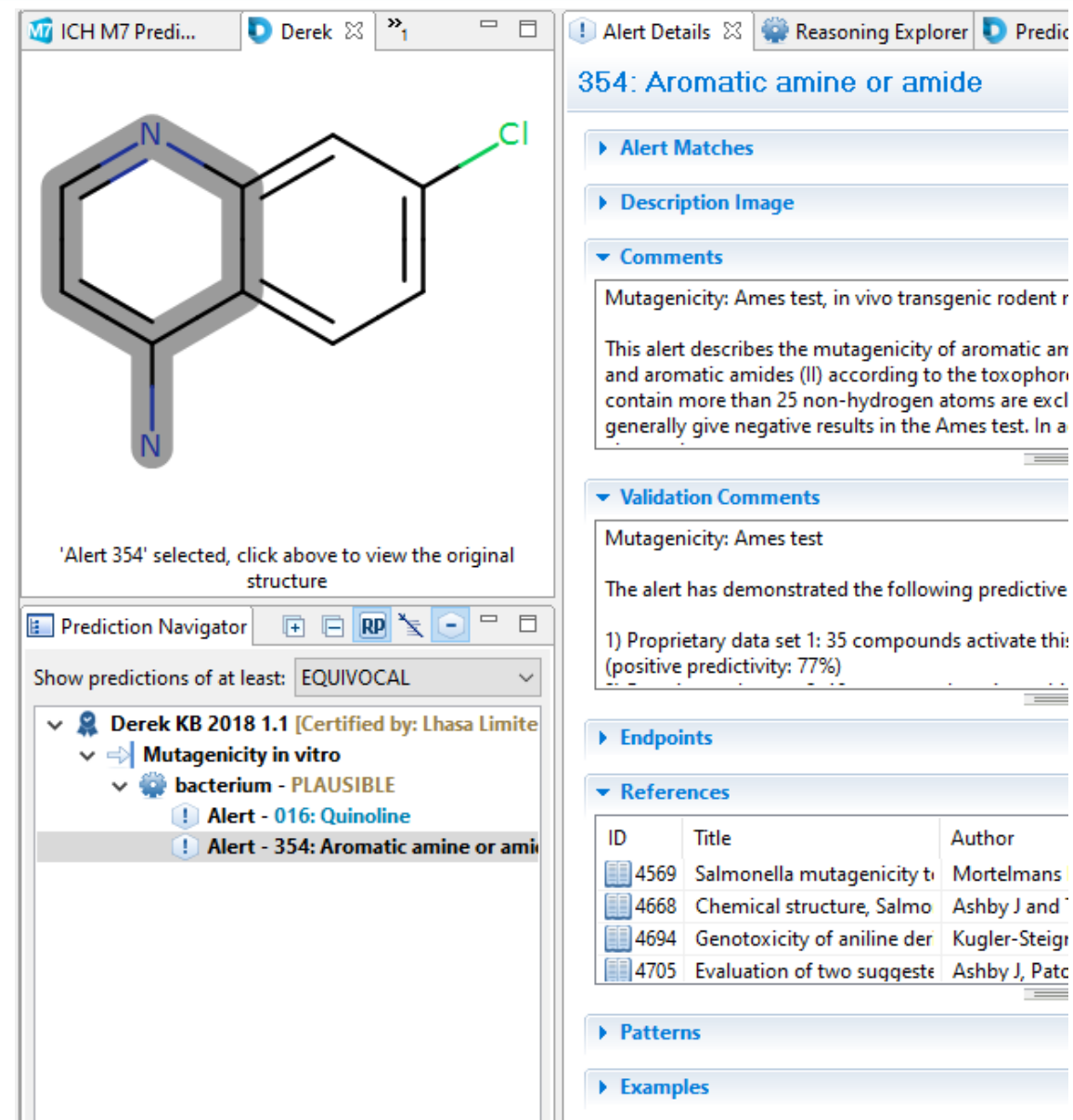
Accepting a
positive
prediction

Relatively easy to accept if
wish to be conservative

Mechanistic rationale

Supporting data

Trust in the model

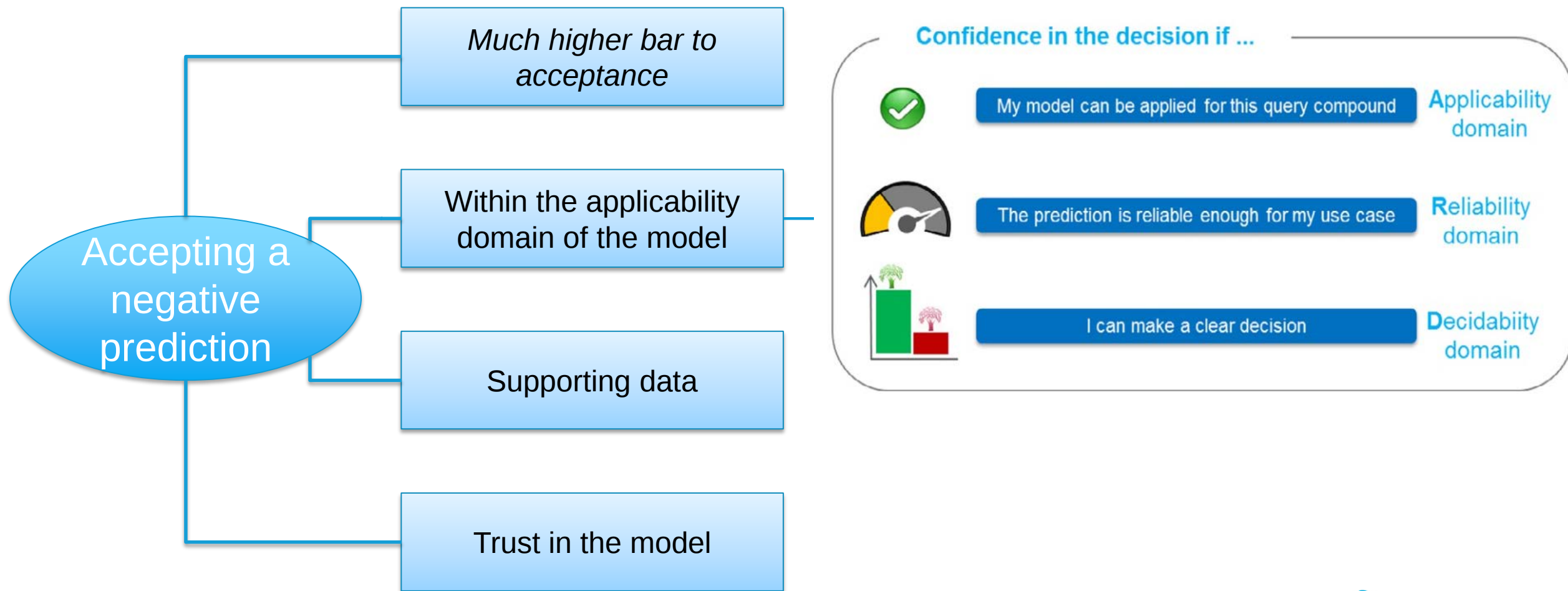


The screenshot displays the Derek software interface. At the top, a chemical structure of 2-chloroquinoline is shown. Below it, a text box states: "'Alert 354' selected, click above to view the original structure". The 'Prediction Navigator' pane on the left shows a tree structure of predictions, with 'Alert - 354: Aromatic amine or amide' selected. The right pane, titled 'Alert Details', shows the following information:

- Alert Details**: 354: Aromatic amine or amide
- Alert Matches**: (link)
- Description Image**: (link)
- Comments**:
 - Mutagenicity: Ames test, in vivo transgenic rodent r
 - This alert describes the mutagenicity of aromatic an and aromatic amides (II) according to the toxophor contain more than 25 non-hydrogen atoms are excl generally give negative results in the Ames test. In a
- Validation Comments**:
 - Mutagenicity: Ames test
 - The alert has demonstrated the following predictive
 - 1) Proprietary data set 1: 35 compounds activate thi (positive predictivity: 77%)
- Endpoints**: (link)
- References**:

ID	Title	Author
4569	Salmonella mutagenicity t	Mortelmans
4668	Chemical structure, Salmo	Ashby J and
4694	Genotoxicity of aniline der	Kugler-Steigr
4705	Evaluation of two suggeste	Ashby J, Patc
- Patterns**: (link)
- Examples**: (link)

Negative prediction accepted from *in silico*



It's difficult, but important, to make negative predictions.
Williams. Reg. Toxicol. Pharmacol., 2016, 76, 79

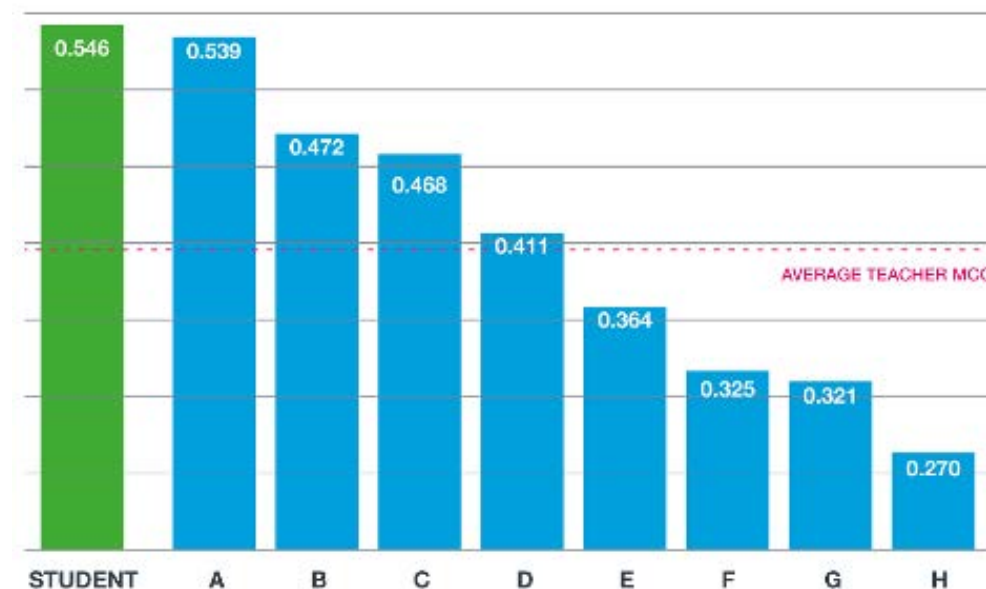
Applicability domain: towards a more formal definition.
Hanser SAR QSAR Environ Res., 2016, 27, 893

Machine learning with proprietary data

- Solving the problem of limited public datasets...
 - Machine learning approach to harvest knowledge from proprietary data
 - <https://www.lhasalimited.org/products/Effiris.htm>
 - Late breaking poster P411, Thurs 08:30am-11:30am, 3595, T. Hanser

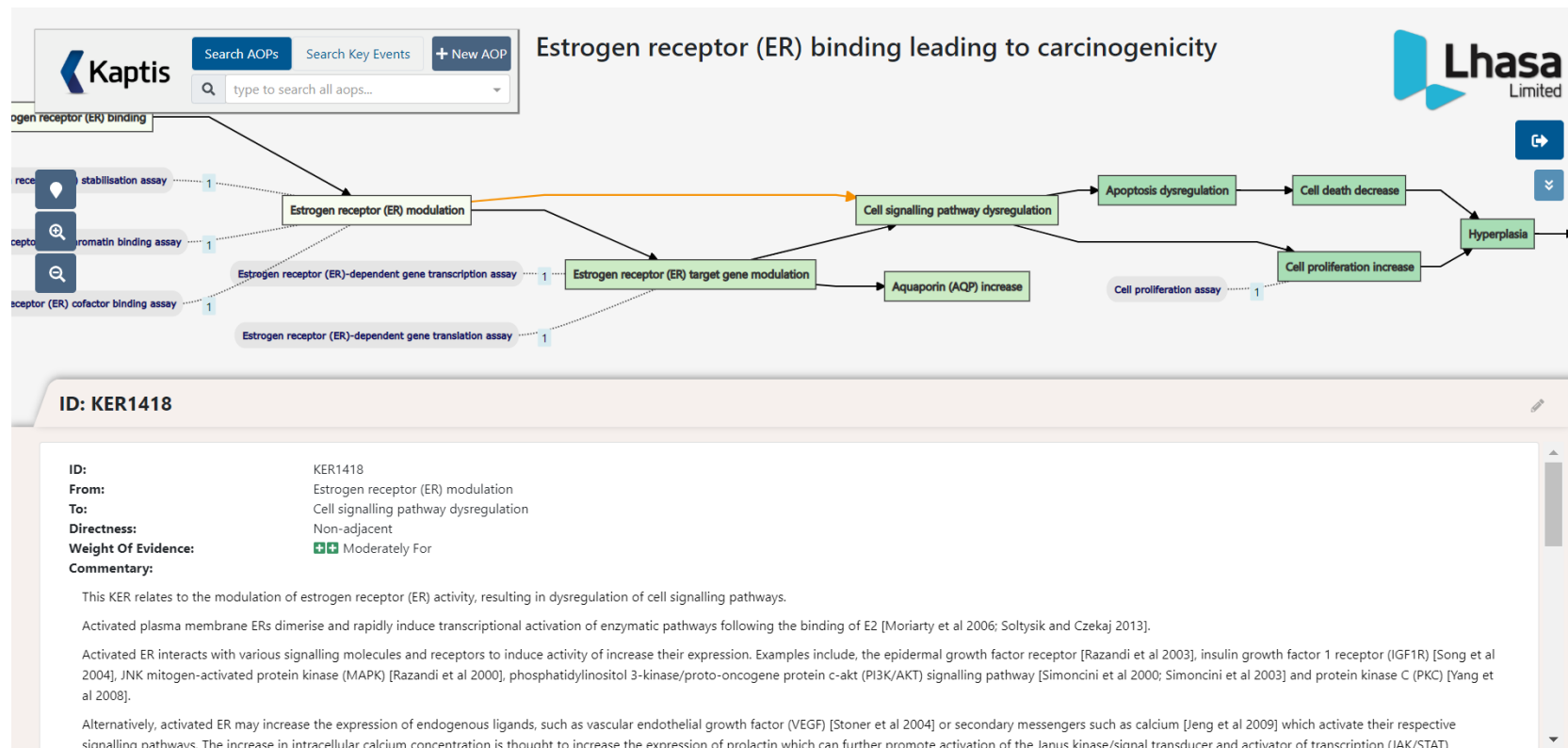
Avoiding hERG-liability in drug design via synergetic combinations of different (Q)SAR methodologies and data sources: a case study in an industrial setting

T. Hanser. [J. Cheminf.](#), 2019, 11, 9



AOPs to reduce the need for animal testing

- Linking assays and models through AOPs
- The Application of Adverse Outcome Pathways (AOPs) for Risk Assessment
 - 17th March, CC Room 205B, 9am-10am



Summary

- *In silico* can play a critical part in risk assessment
 - Reducing costs, animals and uncertainty
- This demands new approaches to machine learning and to defining uncertainty
 - Lhasa is investing in pre-competitive collaborations to address these challenges
- Come and see how you can work with us - Booth 828

Lhasa Limited

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Work
experience

Publications &
presentations

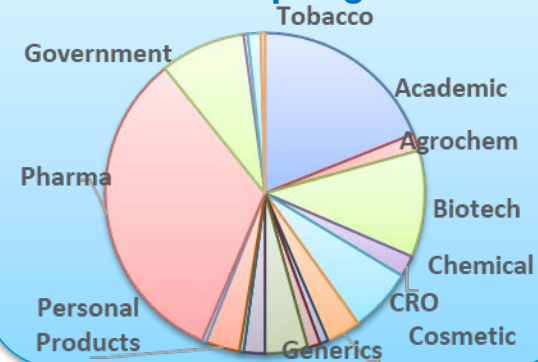
Sponsor
PhDs

Undergrad
projects

Head office in Leeds, UK



A membership organisation



Predictive software (expert & machine learnt)



Purge



Degradation



Toxicity



Metabolism



Regulators & Governmental Agencies (38 are members of Lhasa)

FDA

PMDA

USP

NIHS

MHRA

Data & knowledge sharing Honest broker



Vitic
intermediates



Vitic
excipients



Setaria

MIP-DILI

eTRANSAFE

eTOX

Proprietary data mining

