The application of \textit{in silico} models to support decision making in toxicology

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on behalf of Dr Richard Williams
Our ambition
to eliminate animal studies without compromising safety
and 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

In vivo (animal) studies
- Routine*
- Targeted
- Confirmatory
- Not needed

In vitro studies
- Routine
- Comprehensive
- Targeted
- Confirmatory

In silico studies
- Supportive*
- Comprehensive
- Accepted

Acceptance of non-animal
Acceptance of in silico

“…reducing mammal study requests and funding 30% by 2025 and completely eliminating them by 2035,”
Andrew Wheeler, EPA
Opportunities for *in silico* to support safety decisions

*In silico* is sufficient and accepted when making a safety decision

*In silico* identifies when a safety study is needed

*In silico* informs animal study design
Opportunities for *in silico* to support safety decisions

- **In silico** is sufficient and accepted when making a safety decision
- **In silico** identifies when a safety study is needed
- **In silico** informs animal study design
- Negative prediction accepted from *in silico*
- Positive prediction accepted from *in silico*
- *In vitro + in silico* sufficient to make a decision
- *In silico* to help reduce animal burden
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

Available as a pre-print
ALTEX - Alternatives to animal experimentation.
In vitro + in silico to decide without animals

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

Exclusion criteria → Derek alert outcome → Certain Probable Plausible
   Equivocal Non-sensitiser with misclassified or unclassified features

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

Non-sensitiser
Doubt improbable impossible

1st assay
2nd assay
3rd assay

sensitiser
non-sensitiser

Potency category 1 (GHS 1A)
Potency category 2 (GHS 1A)
Potency category 3 (GHS 1B)
Potency category 4 (GHS 1B)

Potency category 5/6 (GHS no cat)
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

Gold
Negative prediction accepted from *in silico*

Accepting a negative prediction

- **Much higher bar to acceptance**
- Within the applicability domain of the model
- Supporting data
- Trust in the model

Confidence in the decision if...

- My model can be applied for this query compound**
- The prediction is reliable enough for my use case**
- I can make a clear decision

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

It's difficult, but important, to make negative predictions. Williams. Reg. Toxicol. Pharmacol., 2016, 76, 79
What next for \textit{in silico} models?

- \textit{in silico} models must be accurate, transparent and built with an understanding of toxicity

Best achieved by learning from all available data

Requires new methods to learn from proprietary data

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. \textit{J. Cheminf.}, 2019, 11, 9

https://www.lhasalimited.org/products/Effiris.htm
What next for *in silico* models?

- AOPs to hold relationships between *in vitro* assays and adverse outcomes

https://www.lhasalimited.org/products/kaptis.htm
**Summary**

- *In silico* will play an increasingly critical part in risk assessment
  - reducing the number of animals needed to determine human risk
  - helping select the most relevant in vitro alternatives
  - when sufficiently accurate and comprehensive to eliminate animal studies

- The challenge is massive, and no organisation will succeed alone
  - Precompetitive approaches are going to be key
  - Data sharing without disclosing proprietary structures
  - Formally organising mechanistic information in the context of available assays
Lhasa Limited

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Head office in Leeds, UK

A membership organisation

Data & knowledge sharing Honest broker

Predictive software (expert & machine learnt)
- Purge
- Degradation
- Toxicity
- Metabolism

Regulators & Governmental Agencies (38 are members of Lhasa)
- FDA
- NIHS
- PMDA
- USP
- MHRA

Data & knowledge sharing Honest broker
- VitiC
- eTRANSAFE
- eTOX
- MIP-DILI
- Setaria

Proprietary data mining