

Skin  
**Sensitisation**



Have you got it **covered?**

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# Introduction to skin sensitisation

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## Alternative skin sensitisation assessment methods

The prediction of skin sensitisation is a key requirement for a number of chemical safety assessments such as the Registration, Evaluation, Authorisation & restriction of Chemicals (REACH)<sup>1</sup> and the Classification, Labelling and Packaging (CLP) Regulation<sup>2</sup>. The cosmetic industry faces significant challenges driven by the implementation of EU regulation 1223/2009<sup>3</sup> that stipulates that any cosmetic product or ingredient on the EU market is demonstrably safe but that animal experiments must be replaced by alternative methods by March 2013. Thus, there are considerable pressures to reduce and refine the use of animal tests to assess the skin sensitisation potential of chemicals across a number of industries.

Lhasa Limited offers Derek and Vitic for use in skin sensitisation assessment and as an alternative to animal testing.



## for skin sensitisation

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Derek has a well-established and continually researched skin sensitisation endpoint which contains 100 structural alerts\*. The expert rule-based approach of Derek already demonstrates high predictivity for skin sensitisation, even in humans<sup>4</sup>, and effectively performs as well as the standard *in vivo* assays (local lymph node assay and guinea pig maximisation test).

Derek provides an EC3 potency prediction for those compounds which fire a skin sensitisation alert<sup>5</sup>. Derek also contains expert-derived functionality to provide negative predictions for those compounds which do not fire a skin sensitisation alert<sup>6</sup>.

Given the increasing interest in predicting skin sensitisation potential using combinations of different data sources (known as a defined approach to testing and assessment), Lhasa scientists have developed a transparent defined approach (see page 5) using Derek Nexus alerts, negative predictions and EC3 predictions to accurately predict hazard (sensitiser/non-sensitiser) and potency (GHS categories 1A, 1B or nonclassified, and Basketter human potency categories 1-6)<sup>7</sup>.

*\*2020.1 knowledge base*



## for skin sensitisation

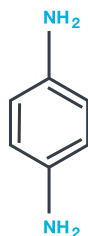
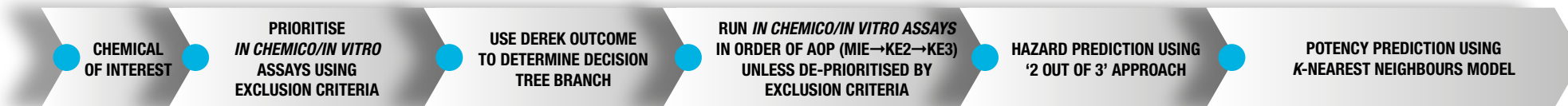
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Vitic is a toxicity database and information management system developed by Lhasa scientists containing expert curated, high-quality, peer-reviewed data from both published and unpublished sources. Directly accessible through the Nexus interface or via a web browser, Vitic provides you with more than 28,000\* skin sensitisation data records for more than 6,000\* structures. With new data being added on a regular basis, this data source provides current skin sensitisation data and supports read-across assessments.

*\*Vitic 2018.1 database*

### **The information held within Vitic has been derived from sources such as:**

- Cosmetic Ingredients Review
- Cronin and Basketter review 1994
- European Chemicals Agency (ECHA)
- European Chemicals Bureau (IUCLID)
- Local lymph node assay data extracted from NICEATM ICCVAM
- OECD Screening Information Dataset (SIDS)
- Scientific Committee on Consumer Products (SCCP)



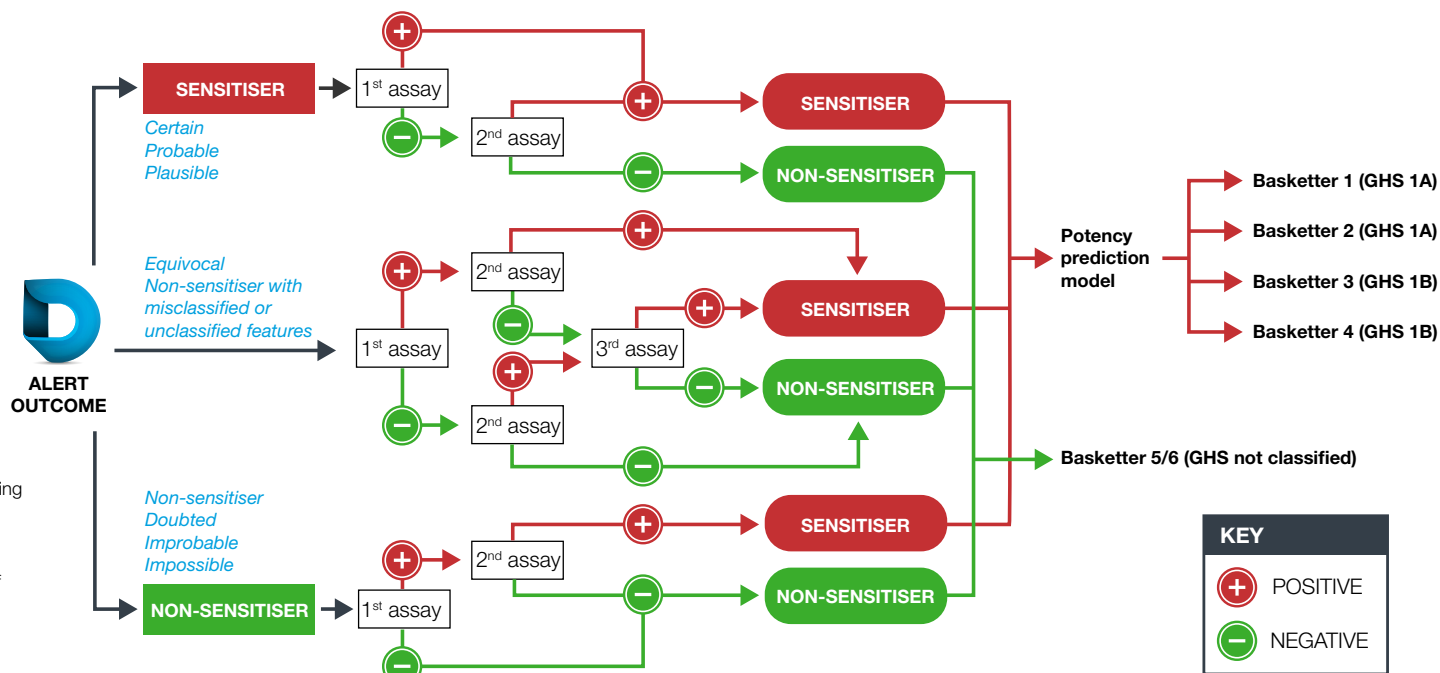
Prioritise ✓ & de-prioritise ✗ assays using exclusion criteria

	MIE*	KE2 <sup>#</sup>	KE3 <sup>§</sup>
Metabolism	✗	✓	✓
Lipophilicity	✓	✗	✗
Lysine Reactivity	✓	✗	✓

\*Assay measuring the Molecular Initiating Event/KE1 of the skin sensitisation Adverse Outcome Pathway (AOP)  
• DPRA

<sup>#</sup>Assay measuring the 2<sup>nd</sup> Key Event of the skin sensitisation AOP  
• KeratinoSens™/LuSens

<sup>§</sup>Assay measuring the 3<sup>rd</sup> Key Event of the skin sensitisation AOP  
• h-CLAT/U-SENS™



# Derek EC3 prediction methodology

Derek gives a quantitative EC3 prediction for compounds that fire a skin sensitisation alert. The prediction is derived from a Nearest Neighbour Model, where the nearest neighbours are taken from a reference set of compounds that exclusively fire the same alert as the query compound. The Tanimoto similarity score is calculated for the nearest neighbours and an EC3 prediction is made. The nearest neighbour compounds are selected from over 650 compounds in the high-quality Lhasa EC3 dataset which has been curated by Lhasa experts.

Fires Alert ●  
Doesn't Fire Alert ●  
Predicted Value ●

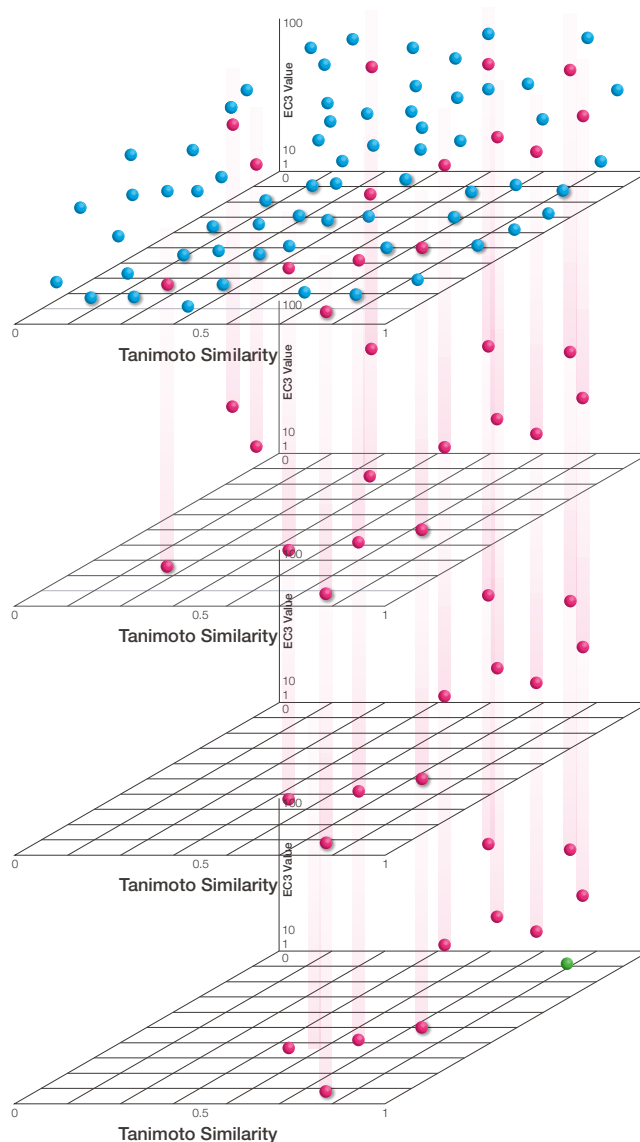


Figure 2  
The Derek Nexus  
EC3 methodology explained

The compounds which fire the same alert as the query compound are highlighted.

The model only considers compounds that fire the alert of interest.

The model calculates the similarity of the compounds, compared to the query. The ten nearest neighbours will be used in the calculation.

These compounds are then used to make a prediction. Expert review of each prediction is recommended and the software allows the addition or removal of compounds by the user to facilitate this.

# Features and benefits



## Transparent Predictions and Graphical Representation Facilitates Expert Assessment

A clear, visual representation of the EC3 prediction is provided. This includes the structures, Tanimoto similarity and EC3 values of the nearest neighbours, as well as the option to display a colour-coded European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC) classification.

EC3 Value	<0.1	≥0.1 to <1	≥0.1 to <10	≥0.1 to <100
Potency Category	Extreme	Strong	Moderate	Weak
GHS	1A - Strong		1B - Other	



## Extensive Coverage of Chemical Space

Derek alerts are built on public, proprietary and regulatory data. Users can also incorporate their own data into Derek thereby generating predictions relevant to their chemical space.



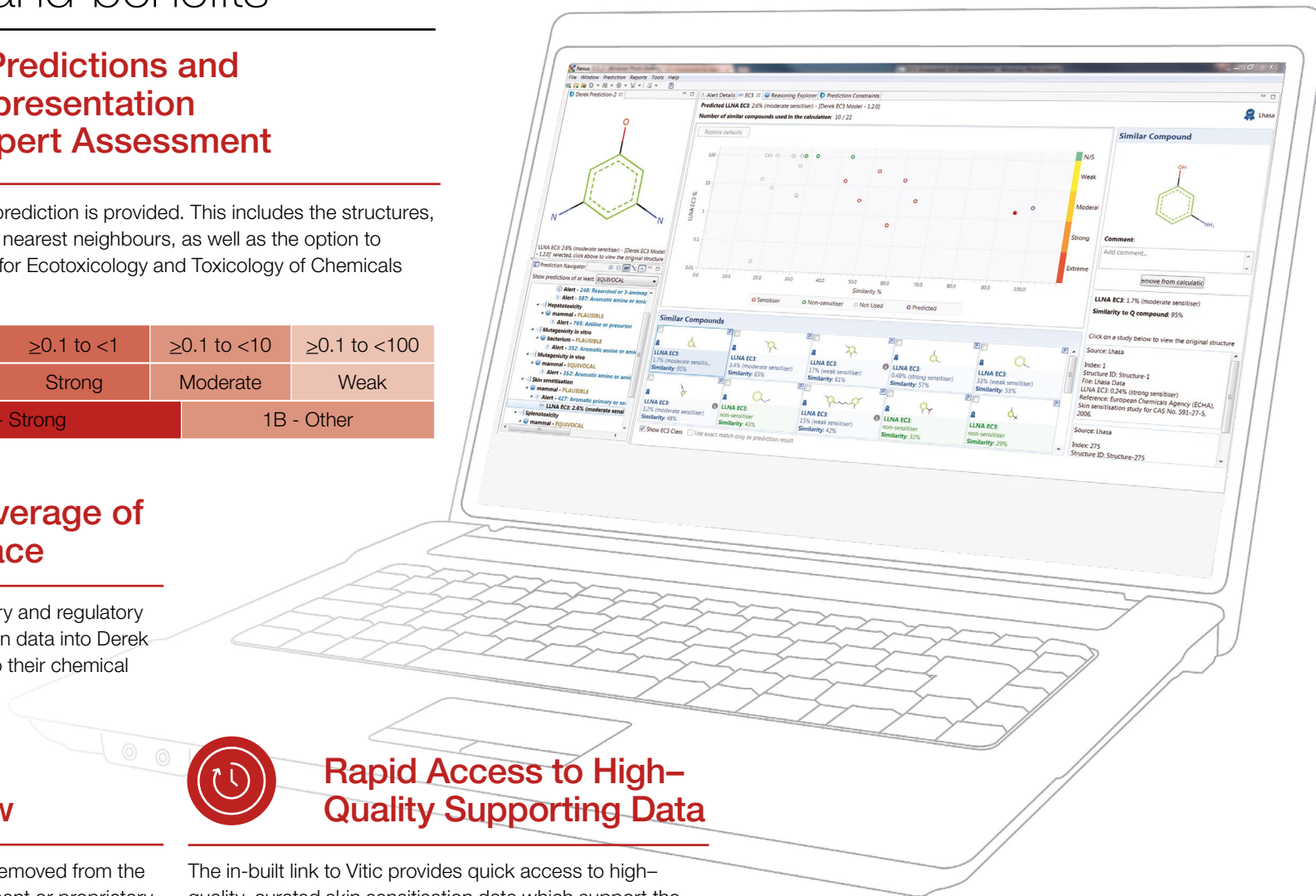
## Interactive Expert Review

Nearest neighbours can be added to or removed from the EC3 prediction based on expert assessment or proprietary knowledge. In addition to this, users can supplement the Lhasa EC3 dataset with their own data to increase the chemical space covered.



## Rapid Access to High-Quality Supporting Data

The in-built link to Vitic provides quick access to high-quality, curated skin sensitisation data which support the prediction and read-across assessments.



# Features and benefits



## Reduce Animal Use

Regulations such as EU regulation 1223/2009 prohibit the use of animal testing for cosmetic ingredients. The use of Derek as part of a Defined Approach can deliver predictions that have a high concordance with the LLNA assay and provides a significant step forward in assessing skin sensitisation.



## Negative Predictions Provided

Rather than an “Out of Domain”, Derek provides negative predictions for the skin sensitisation endpoint when query compounds do not fire any skin sensitisation alerts.



## A Derek Alert is a Lhasa Alert

All Derek skin sensitisation alerts are developed in-house by a dedicated team of expert scientists in consultation with industry experts. Lhasa’s investment in research ensures that alerts are regularly updated and based on current toxicological knowledge.



## Fill your Data Gaps

The use of Derek with *in chemico/in vitro* assays can predict the skin sensitisation potential of chemicals including those outside the applicability domain of existing non-animal assays<sup>6</sup>.



# Our Products

What software do we produce?

Through regular scientific and software updates, Lhasa continues to deliver accurate, transparent knowledge to its solutions, to make them more comprehensive, as well as easier and faster to use.

Lhasa offers some of its products on the Lhasa Cloud. This means new features can be delivered even faster, giving members immediate access to cutting-edge science. Find out more about our products at:

<https://www.lhasalimited.org/products>



**Derek**<sup>®</sup>  
nexus

*An expert rule-based system for the prediction of toxicology.*



**Sarah**<sup>®</sup>  
nexus

*A statistical-based system for the prediction of mutagenicity.*



**Setaria**<sup>®</sup>  
nexus

*A project-centric database for storage of toxicity knowledge.*



**Mirabilis**<sup>®</sup>  
nexus

*A tool for assessing the relative purging of mutagenic impurities.*



**Zeneth**<sup>®</sup>  
nexus

*An expert rule-based system for the prediction of degradation pathways.*



**Vitic**<sup>®</sup>  
nexus

*A chemical database and information management system.*



**Meteor**<sup>®</sup>  
nexus

*An expert rule-based system for the prediction of metabolic fate.*



**Effiris**<sup>™</sup>  
nexus

*A secondary pharmacology model suite leveraging value from federated learning.*



**Kaptis**<sup>™</sup>  
nexus

*A tool to support risk assessment in the context of adverse outcome pathways.*

## References

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• <https://echa.europa.eu/testing-clp>

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<http://dx.doi.org/10.1016/j.yrtph.2016.01.009>

• Macmillan D. and Chilton M. L. (2019) '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', Regulatory Toxicology and Pharmacology, vol. 101, February, pp. 35-47.

<https://bit.ly/2Zmixv4>

# Working together for a better future

When asked why people choose to work with Lhasa Limited, the common responses are:



Software is easy to use and well supported.



Transparency of Lhasa systems allows trust and confidence in the science presented.



Over 35 years of experience in developing state-of-the-art *in silico* prediction and database systems.



All science is developed in-house, providing the opportunity to discuss directly with Lhasa expert scientists.



Lhasa collaborates with the wider scientific community to advance the understanding and performance of *in silico* technology.



Feedback from members is encouraged and listened to, and drives the future development of Lhasa products.

shared knowledge • shared progress



[www.lhasalimited.org](http://www.lhasalimited.org)

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