Lhasa Limited is a developer of expert knowledge based prediction software and chemical databases.
Agenda

- Introduction to Lhasa Limited
- Derek Nexus
  - What is it?
  - Who uses it and how?
Lhasa Limited is a developer of expert knowledge based prediction software and chemical databases.
Who are Lhasa Limited?

- Established in 1983
- Located opposite Leeds University, UK
- Not-for-profit organisation and charity
- Controlled by membership group
- Knowledge base and database systems
Derek users
Current members

A
- Abbott Healthcare Products B.V.
- AbbVie Inc.
- Aclairo
- Actelion Pharmaceuticals Ltd.
- Ajinomoto Pharmaceuticals Co., Ltd.
- AkzoNobel
- Alexza Pharmaceuticals Inc.
- Allos BioPharma
- Alkermes
- Almirall, S.A.
- Amgen Inc.
- Anacor Pharmaceuticals Inc.
- Anadolu University
- ANSES (French Agency for Food, Environmental and Occupational Health Safety)
- Aptuit - Verona
- Ardea Biosciences
- Array BioPharma Inc.
- Asahi Kasei Pharma Corporation
- Askia Pharmaceutical
- Astellas
- Astrazeneca
- Aurobindo Pharma Limited
- Avon Products Inc.

B
- Basilea Pharmaceutica Ltd.
- Bayer CropScience
- Bayer Healthcare Pharmaceuticals
- Beiendorf
- Belgian Scientific Institute of Public Health
- Bioclin Limited
- Biogen
- Biomolecular Simulations Ltda
- Boehringer Ingelheim Pharma GmbH & Co. KG
- Boehringer Ingelheim Austria GmbH
- BP Global
Collaboration

International Collaborative Group Meetings 2013

USA ICGM
San Antonio, USA
14th March 2013

Japan ICGM
Hosted by CTC Laboratory Systems
Tokyo, Japan
November 2013
Other collaborations:

**FDA**
- Research Collaboration Agreement

**OECD Toolbox PII**
- Adverse Outcome Pathways

**eTOX**
- eTOX database

**MIP DILI**
- DILI database

**Vitic:**
- Intermediates
- Excipients
- Aryl Boronic acids
- Aromatic Amines
What is Derek Nexus?

- Toxicity Prediction Tool
- Uses Knowledge Base to:
  - Match parts of the query structure (toxicophores) to alerts
  - Apply Reasoning to Assess the likelihood for a prediction
  - Give an overall prediction of toxicity for selected species
  - Store custom knowledge
What causes a prediction?

Matches parts of query structure with alerts in the knowledge base
What causes a prediction?

- Matches parts of query structure with alerts in the knowledge base

Alert 001: Alpha-Halo ketone

\[ R1 = \text{Cl, Br, I} \]

Toxicophore
What causes a prediction?

Matches parts of query structure with alerts in the knowledge base.

Alert firing depends on:
- Structure - defined by pattern in knowledgebase.
  - Endpoint prediction depends on:
    - Alert
    - Species
    - Physicochemical properties
    - Other Endpoints (extrapolation)
What is an alert?

An alert is a set of structural features in a molecule, that make a toxicologist suspect that the substance may show a particular effect.
<table>
<thead>
<tr>
<th>Fact/Property</th>
<th>Value</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>LogP</td>
<td>The value of LogP can...</td>
<td></td>
</tr>
<tr>
<td>LogKp</td>
<td>The value of LogKp can...</td>
<td></td>
</tr>
<tr>
<td>Average Molecular Mass</td>
<td>0</td>
<td>Lhassa Limited, version 1.0</td>
</tr>
</tbody>
</table>
\begin{align*}
\text{Structure:} & \quad \text{C} & \text{C} & \text{C} & \text{C} & \text{C} \\
\text{Problems:} & \quad \text{LogP} & 2.05 & \text{BioByte Corp., version 5.3} \\
\text{} & \quad \text{LogKp} & -2.07 & \text{Potts & Guy, version 1.0 (LogP, BioByte Corp., version 5.3; Average Molecular Mass, Lhasa Limited, version 1.0)} \\
\text{} & \quad \text{Average Molecular Mass} & 132.16 & \text{Lhasa Limited, version 1.0}
\end{align*}
Query compound

Toxicophore

Predicted toxicity
**Alert description**

This alert describes the skin sensitisation of alpha,beta-unsaturated aldehydes and precursors which interact with skin proteins via a Michael addition mechanism (Patlewicz et al.). Beta-disubstituted alpha,beta-unsaturated aldehydes are less susceptible to Michael addition and are thought to react via a Schiff base mechanism (Patlewicz et al.). The activity of such compounds is described elsewhere in the knowledge base.

**Comments**

Skin sensitisation activity for alpha,beta-unsaturated aldehydes and their precursors has been demonstrated in various assays including the guinea pig maximisation test (Cromin and Baskette) and the mouse local lymph node assay [Patlewicz et al.]. Skin sensitisation in

**Literature references**

1. [A comparison of the local lymph node test and an inflammation test for use in skin sensitisation studies](https://doi.org/10.1016/0202-8538(92)90084-3)
   - Source: *Archives of Toxicology* 1992
   - Year: 1992

2. [Multivariate QSAR analysis of a skin sensitisation dataset](https://doi.org/10.1515/1-56081-9909-082)
   - Source: *Chemical Research in Toxicology* 1994
   - Year: 1994

**Example compounds**

- Dichloro-2-methylpropene
- Alpha-methylcinnamic acid
- 2,6-Heptadienal
- Trans-2-hexenal diethyl
Batch process multiple compounds
After processing (single or batch)
Output reports in various formats:
- doc
- pdf
- html
- ppt
- csv
- txt
- sdf
- xml

Reports

<table>
<thead>
<tr>
<th>Alert Locations</th>
<th>Compound Name</th>
<th>Endpoints</th>
<th>Species</th>
<th>Likelihood</th>
<th>Alert Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4,6 trinitro fluoro benzene</td>
<td>Mutagenicity in vitro</td>
<td>bacterium</td>
<td>PLAUSIBLE</td>
<td>Aromatic nitro compound</td>
<td></td>
</tr>
<tr>
<td>2,4,6 trinitro fluoro benzene</td>
<td>Mutagenicity in vitro</td>
<td>bacterium</td>
<td>PLAUSIBLE</td>
<td>Aromatic nitro compound</td>
<td></td>
</tr>
<tr>
<td>2,4,6 trinitro fluoro benzene</td>
<td>Mutagenicity in vitro</td>
<td>bacterium</td>
<td>PLAUSIBLE</td>
<td>Aromatic nitro compound</td>
<td></td>
</tr>
<tr>
<td>2,4,6 trinitro fluoro benzene</td>
<td>Skin sensitization</td>
<td>mammal</td>
<td>PLAUSIBLE</td>
<td>Activated benzene</td>
<td></td>
</tr>
<tr>
<td>2,4,6 trinitro fluoro benzene</td>
<td>Phototoxicity</td>
<td>mammal</td>
<td>PLAUSIBLE</td>
<td>Carcinogenic</td>
<td></td>
</tr>
<tr>
<td>8-methylcoumarin</td>
<td>Phototoxicity</td>
<td>mammal</td>
<td>PROBABLE</td>
<td>Coumarin</td>
<td></td>
</tr>
<tr>
<td>Aminothiazine</td>
<td>Chromosome damage in vitro</td>
<td>mammal</td>
<td>PLAUSIBLE</td>
<td>Acridine or analogue</td>
<td></td>
</tr>
<tr>
<td>Aminothiazine</td>
<td>Hepatotoxicity</td>
<td>mammal</td>
<td>PLAUSIBLE</td>
<td>Quinolinol</td>
<td></td>
</tr>
</tbody>
</table>
How do people use Derek?

- Occupational Toxicity
  - Label predicted skin sensitisers

- High throughput screening
  - Filter out likely toxic compounds early

- Candidate selection and modifications
  - Toxicity testing vs candidate selection
  - Structure refinement?
How do people use Derek?

- Assessing Impurity Toxicity
  - ICHM7 guidelines
  - Impurities limited or toxicity tested

- REACH legislation
  - Where little/no toxic information available
  - Fill data gaps
  - Complete QMRF and QPRF reports
Thank you!

For further information please consult: www.lhasalimited.org

or

Contact: info@lhasalimited.org