Examples of expert computer systems for toxicity and metabolism prediction

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Lhasa Limited: What We Do

shared knowledge shared progress

Ve Vitic excipients
Vi Vitic intermediates
eTOX
iPIE
Proprietary Toxicity And Metabolism Data In Cosmetics

• We need to maximise the use of existing toxicity and metabolism data for cosmetics to optimise in silico model performance in this chemical space

• How much relevant proprietary data do cosmetics companies hold in their archives?

• What barriers exist for sharing these data?
  • Commercial
  • Accessibility

• How can these be overcome?
**In Silico Tool Use Case**

- **Sufficient experimental data available?**
  - **Y**: Perform safety assessment
  - **N**: Suitable for TTC approach?
    - **Y**: Perform safety assessment
    - **N**: Generate experimental/in silico AOP event profile

- **AOP event identified?**
  - **Y**: Perform specific in chemico/vitro tests
  - **N**: Perform general in vitro tests
    - **Y**: Perform read across or de novo safety assessment
    - **N**: In silico tool

**Database**
Expectations For An *In Silico* Tool?

- Industry standard
- Validation
- Scientific updates
- Software maintenance
- Support and training
- Free at the point of use
**In Silico Tool Use Case**

- Sufficient experimental data available? 
  - Y: Perform safety assessment
  - N: Perform read across or de novo safety assessment
  
- Suitable for TTC approach? 
  - Y: Derek Nexus in AOP event profile generation
  - N: Meteor Nexus as a complement to incompletely metabolically competent (Q)SARs and in chemico/vitro tests

- Generate experimental/in silico AOP event profile

**In silico tool**

**Database**
Example Derek Nexus Prediction

Displaying 'Alert 019', click above to view the original structure.

019: Epoxide

Alert Matches

Description Image

Comments

Epoxides are electrophilic compounds that readily bind to DNA [Citti et al., Sugiura and Goto]. As a consequence, they may exhibit mutagenicity in the Ames test, generally in strains TA100 and TA1535 without S9 mix [Canteri et al., von der Hude et al., Sugiura and Goto, Tamura et al., Wade et al]. The effect of S9 mix on the mutagenic response varies depending, for example, on the susceptibility of the test chemical to detoxification by epoxide hydrolases and glutathione S-transferase present in the S9 mix [Cestelain et al.].

Validation Comments

The alert has demonstrated the following predictive performance:
1) Proprietary data set 1: 4 compounds activate this alert of which 3 are reported positive (positive predictivity = 75%)
2) Proprietary data set 2: 1 compound activates this alert of which 1 is reported positive (positive predictivity = 100%)
3) FDA CSFAN data set: 304 compounds activate this alert of which 229 are reported positive (positive predictivity = 75%)

Endpoints

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<th>ID</th>
<th>Name</th>
<th>Parent</th>
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<tbody>
<tr>
<td>4150</td>
<td>Mutagenicity</td>
<td>Mutagenicity (ALL)</td>
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References

<table>
<thead>
<tr>
<th>ID</th>
<th>Title</th>
<th>Author</th>
<th>Source</th>
<th>Year</th>
<th>Supplement</th>
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<td>516</td>
<td>Studies for a genotoxic potential of some...</td>
<td>Lang R and Reimann R.</td>
<td>Environmental and Molecular Biology</td>
<td>1993</td>
<td>DOI: 10.1002</td>
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</table>
How Derek Nexus Works

Knowledge base

- Alert dictionary
- Example compounds
- Rule base

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Rules

- Assign likelihood of toxicity based on the presence of a structural alert or matching example compound, including consideration of species effects.
- Describe the likelihood of toxicity based on other types of relationship such as associations between endpoints.
- Multiple arguments for and against the toxicity of a chemical are weighed up by a reasoning engine.

What Can Derek Nexus Contribute?

- AOP event profile predictions
  - Transparent
  - Expert opinion with supporting evidence

- AOP outlines
  - Events and tests
  - Expert opinion with supporting evidence
Derek Nexus Endpoints

• 70 endpoints in Derek Nexus are organised hierarchically

- Chemical structure & properties
- Molecular initiating event
- Cellular response
- Organ response
- Organism response

• Endpoint predictions may correspond to different AOP levels depending on available evidence

- Mutagenicity
- Skin sensitisation
Derek Nexus Endpoints

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<table>
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<tr>
<th>Chemical structure &amp; properties</th>
<th>Molecular initiating event</th>
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<td></td>
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<tr>
<td>Cholinesterase inhibition</td>
<td>Mutagenicity</td>
<td>a2u-Globulin nephropathy</td>
<td>Skin sensitisation</td>
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<tr>
<td>HERG channel inhibition</td>
<td>Mitochondrial dysfunction</td>
<td>Hepatotoxicity</td>
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</tbody>
</table>

- Valid endpoints:
  - Carcinogenicity (ALL)
  - Genotoxicity (ALL)
  - Irritation (ALL)
  - Miscellaneous endpoints (ALL)
  - Neurotoxicity (ALL)
  - Organ toxicity (ALL)
  - Reproductive toxicity (ALL)
  - Respiratory sensitisation (ALL)
  - Skin sensitisation (ALL)
What Can Derek Nexus Contribute?

• AOP event profile predictions
  • Transparent
  • Expert opinion with supporting evidence

• AOP outlines
  • Events and tests
  • Expert opinion with supporting evidence
A number of pharmaceutical drugs have been shown to block the HERG potassium channel current in whole-cell patch clamp electrophysiology assays in a variety of cell types...

HERG encodes for the alpha-subunit of a potassium channel which is thought to carry the rapid component of the delayed rectifier current IKr in the heart [Mitcheson et al, Tristani-Firouzi and Sanguinetti]. Blocking of this channel can lead to the lengthening of the ventricular repolarisation phase in the heart, and is characterised on the electrocardiogram (ECG) as a prolongation of the QT interval [Crumb and Cavero]. ...

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Mapping Derek Nexus Knowledge To AOPs

Chemical structure & properties
Molecular initiating event
Cellular response
Organ response
Organism response

PPAR activation
Induction: acyl coA oxidase
CYP4504A
Proliferation*:
peroxisome smooth ER

Liver: hyperplasia*
hypertrophy*
tumours

In rats and mice but not in humans

*Repeat dose study
Expert derivation of alerts is slow

All endpoints: use statistical/machine learning tools to facilitate alert identification

Interpretation of no alerts?

Bacterial mutagenicity: use feature analysis of reference data set to support negative predictions

Predictions are qualitative

Skin sensitisation: modelling of LLNA EC3 potency within existing alert classes
Derek Nexus Potential Future Enhancements

• AOP event profile prediction
  • Improved endpoint definitions
    • eTox ontologies
  • Facilitated learning of biological plausibility
    • Support chemical class-adverse outcome associations

• AOP representation
  • Structured AOP content
  • Synchronisation of AOP content with AOP Knowledge Base
    • Standard AOP exchange format
    • Acceptance of AOP breadth versus depth
Example Meteor Nexus Prediction
Metabolic path for selected metabolite including identification of potentially adduct-forming and other intermediates.
How Meteor Nexus Works

Knowledge base

- Biotransformation dictionary
- Example reactions
- Rule base

All reactions which could occur

How likely a reaction will occur

Probable
- Plausible
- Equivocal
- Doubted
- Improbable

What Can Meteor Nexus Contribute?

- Assessment of metabolically-mediated toxicity complementary to that from a (Q)SAR toxicity model
  - All or any metabolites can be passed directly to Derek or Sarah Nexus for analysis
  - Identification of potentially adduct-forming intermediates

- Whilst consideration of metabolism is implicit in many (Q)SAR toxicity models, gaps will exist
  - Assay on which model is based is metabolically incomplete or incompetent
  - Metabolic precursors may not be adequately represented in experimental data
  - Metabolic relationships between different structural classes may not be established
Meteor Nexus: Recent Work

Knowledge base
- Biotransformation dictionary

Database
- Known metabolic reactions

Proprietary Database
- Known metabolic reactions

Expert system
All reactions which *could* occur

Machine learning
How likely a reaction *will* occur

Precision

Processing constraint
Metabolite Toxicity View

Likely:
- non-mutagenic

Unlikely:
- mutagenic

Query chemical
Meteor Nexus Potential Future Enhancements

• Meaningful specific models
  • Species
  • Target organ

• Quantification of metabolites

• Limited by data availability
Conclusions

• (Q)SARs for toxicity and metabolite prediction can contribute to the generation of AOP event profiles
  • Low to medium molecular weight organics; inorganics
  • Manual curation and transparency associated with expert systems lend them to the representation of such predictions in an AOP context
• We need to make the most of existing toxicity and metabolism data and knowledge
  • Both capture and exchange
• All stakeholders need to be engaged to ensure use cases are adequately addressed and solutions acceptable to all
Questions