An Extended Mechanistically-Based *In Silico* Profiler for Liver Toxicity

M.T.D. Cronin1, B. Bienfait2, T. Magdzia2, D. Ebbrell1, S.J. Enoch1, J.W. Firman1, J.C. Madden1, A. Mostrag1, J. Rathman1,4, V. Vitcheva1, C. Yang2,3

1School of Pharmacy and Biomolecular Sciences, Liverpool John Moores University, Liverpool, England; 2Molecular Networks GmbH, Nuremberg, Germany; 3Altamira LLC, Columbus OH, USA; 4Department of Chemical and Biomolecular Engineering, The Ohio State University, Columbus OH, USA

*m.t.cronin@ljmu.ac.uk*

---

The Problem: *In Silico* Repeated Dose Toxicity Assessment

- *In silico* methods (Quantitative Structure-Activity Relationships ([Q]SARs) and read-across) can fill data gaps where toxicological information is missing.

- Toxicity from low and repeated dose exposure is acknowledged as being difficult to predict *in silico*.

- *In silico* prediction of organ level toxicity is one means of deriving No Observed (Adverse) Effect Levels (NOAELs; adverse effects to the liver drive many NOAELs).

- This study aimed to extend an *in silico* profiler for liver toxicity by compiling existing knowledge and placing it in a mechanistic framework.

---

Methods and Resources Utilised

- Information on mechanisms of liver toxicity was retrieved through literature searches and organised in terms of chemistry relating to MIEs.

- COSMOS DB – Where possible, mechanistic information was supported by *in vivo* data relating to liver toxicity which were extracted from the COSMOS database (go to cosmobdb.eu).

- AOP Wiki – Anchorage to available AOPs and MIEs.

- The ChemTyper (chemotyper.org), as well as use of clustering and grouping, was used to identify relevant molecular fragments (chemotypes).

- Relevant chemotypes were designed and implemented as CSRML with imbedded physicochemical properties or as SMARTS.

- Physicochemical Properties calculated: hydrogen bond acceptors, hydrogen bond donors, - molecular weight, log P, total polar surface area, number of rotatable bonds, eccentric connectivity index, vertex adjacency matrix.

---

**Table 1. *In Silico* Profilers for Liver Toxicity**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Molecular Initiating Event(s)</th>
<th>Adverse Effects</th>
<th>Number and Types of Alerts</th>
<th>Indicative AOPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reactive Hepatotoxicity</td>
<td>Covalent binding</td>
<td>Fibrosis</td>
<td>&gt; 100 Structural Alerts (SAs)</td>
<td>#38 Protein</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>alkylation leading to liver fibrosis</td>
</tr>
<tr>
<td>Mitochondrial Dysfunction</td>
<td>Disruption of proton gradient</td>
<td>Liver inflammation</td>
<td>&gt; 20 SAs 26 csrml alerts</td>
<td>#144 Lysosomal</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>damage leading to liver inflammation</td>
</tr>
<tr>
<td>Nuclear Receptor Disruption</td>
<td>Binding to Nuclear Receptors e.g. LXR, PPAR</td>
<td>Steatosis</td>
<td>&gt; 100 SAs 756 csrml alerts</td>
<td>#34 LXR activation leading to hepatic steatosis</td>
</tr>
<tr>
<td>Phospholipidosis</td>
<td>Trapping of molecules within lysosomes</td>
<td>Excess accumulation of phospholipids</td>
<td>&gt; 30 SAs 45 csrml alerts</td>
<td>None available</td>
</tr>
<tr>
<td>General Liver Toxicity</td>
<td>Multiple, often uncharacterised</td>
<td>Often undifferentiated</td>
<td>&gt; 20 16 csrml alerts</td>
<td>None available</td>
</tr>
</tbody>
</table>

---

Conclusions and Recommendations

- Over 100 alerts are provided for liver toxicity that form an *in silico* profiler.

- The profiler can be used to group chemicals according to mechanism of action.

- Such AOPs that exist for (non-carcinogenic) liver toxicity proved to be valuable resources to develop profilers.

- AOPs assisted in the understanding of MIEs; future work could use NAMs to develop the profilers further.

- Further development of profilers will be attempted as mechanisms (and AOPs) are described.

- Tools such as COSMOS DB / TOXGPS are a valuable resource to pull together toxicological information and knowledge.

---

References


Acknowledgement

Funding from Cosmetics Europe Long Range Science Strategy (LRSS) Programme