Mode of Action-based classification model for repeated dose liver toxicity

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Introduction and Aims

The objective of this case study is to develop a Mode of Action (MoA)-based classification model, which should allow correct discrimination between hepatotoxic and non-hepatotoxic chemicals. The poster will present the strategy behind the chemical selection and the initial steps regarding the experimental design. The chemical selection was governed by the following criteria: selection of highly reliable positive and negative hepatotoxins in the 3:1 ratio, with high structural diversity and known toxicogenomics data, covering well the cosmetics structural space as well as overlapping with other Seurat-1 projects. A well characterised in vitro liver system (HepaRG cells) will be exposed to selected reference compounds (90) in a repeated dose exposure scenario using high-throughput screening. The MoA knowledge behind three liver adverse outcomes (fibrosis, steatosis, cholestasis) is used to identify key events that will be chosen as in vitro endpoints to be measured. The read-out of the selected in vitro endpoints will be performed using High Content Screening assay. Based on the obtained experimental data, classification models will be built and compared amongst each other based on their ability to correctly identify negative compounds (negative predictivity).

Theoretical description of Cmax and AUC

Goal: keep the chemical concentration to which cells are exposed relatively constant over time - continuous exposure - in order to maximize the chances for obtaining an in vitro response regardless of whether a measured effect (endpoint) is established through Cmax or AUC type of behaviour.

Expected outcomes

It is foreseen that the resulting classification model will be useful for:

a) The hazard profiling of large datasets.

b) Priority setting (for further testing).

c) Preliminary risk assessment by associating different thresholds of toxicological concern (TTC) with chemicals that are predicted as positive and negative (positive chemicals will be associated with a lower TTC value; negative chemicals with a higher TTC value).