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Machine Learning Prediction of Cyanobacterial Toxin (Microcystin) Toxicodynamics in Humans

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Microcystins (MC) represent a family of cyclic peptides with approx. 250 congeners, some of which were demonstrated to be toxic to humans. The toxicological profile of MC is characterized by the active cellular uptake of MC via organic anion transporting polypeptides (OATPs), and the subsequent irreversible inhibition of primarily ser/thr protein phosphatases (PPP) amongst a number of cellular proteins. Although a comparison between rodents and humans demonstrated that rodents are poor surrogates for humans with regard to the i) type of OATP expressed in the various tissues, ii) the affinity and iii) capacity of expressed OATPs for specific MC congener transport, risk assessment is still based on a single MC congener and a 90-day toxicity study in mice. The observation that humans demonstrate major differences in OATP expression and thus susceptibility to MC only compounded the fact that current risk assessment premises could severely underestimate the potential toxicities of MC due to their congener-specific kinetics. In view of the ever-increasing number of identified MC congeners, yet lacking the ability to synthetize these in sufficient purity and amounts for *in vitro* or *in vivo* testing, an *in silico* approach using toxicodynamic data could provide a first step towards a better toxicity assessment of uncharacterized MCs with relevance for humans. Accordingly, the aim of this study was to develop a comprehensive dataset of toxicodynamics, i.e., the PPP inhibitory capacities of a limited number of MC congeners. These *in vitro* data were then used as a comparative basis driving an *in silico* approach using machine learning (ML). The inhibition of PPP1, PPP2A and PPP5 by 18 structurally different MC was determined and demonstrated MC congener-dependent inhibition activity and a lower susceptibility of PPP5 to inhibition than PPP1 and PPP2A. The data were employed to train a ML algorithm that allows prediction of PPP inhibition (toxicity) based on 2D chemical structure of MC. IC50 values were classified into three toxicity classes, and three ML models were used to predict the toxicity class, resulting in 80-90% correct toxicity predictions, thereby providing an initial step towards in silico hazard predictions for MC and thus a basis for improved risk assessment.