Computational methods for analyzing dioxin-like compounds and identifying potential aryl hydrocarbon receptor ligands - multivariate studies based on human and rodent in vitro data

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt förvar i KB.E3.01 (Lilla Hörsalen), KBC-huset, Umeå Universitet, torsdagen den 19 oktober, kl. 13:00.

Avhandlingen kommer att förvaras på engelska.

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Abstract
Polychlorinated dibenzo-\(p\)-dioxins/dibenzofurans (PCDD/Fs) and polychlorinated biphenyls (PCBs) are omnipresent and persistent environmental pollutants. In particular, 29 congeners are of special concern, and these are usually referred to as dioxin-like compounds (DLCs). In the European Union, the risks associated with DLCs in food products are estimated by a weighted sum of the DLCs’ concentrations. These weights, also called toxic equivalency factors (TEFs), compare the DLCs’ potencies to the most toxic congener, 2,3,7,8-tetrachloro-dibenzo-\(p\)-dioxin (2378-TCDD). The toxicological effects of PCDD/Fs and PCBs are diverse, ranging from chloracne and immunological effects in humans to severe weight loss, thymic atrophy, hepatotoxicity, immunotoxicity, endocrine disruption, and carcinogenesis in rodents.

Here, the molecular structures of DLCs were used as the basis to study the congeneric differences in \textit{in vitro} data from both human and rodent cell responses related to the aryl hydrocarbon receptor (AhR). Based on molecular orbital densities and partial charges, we developed new ways to describe DLCs, which proved to be useful in quantitative structure-activity relationship modeling. This thesis also provides a new approach, the calculation of the consensus toxicity factor (CTF), to condense information from a battery of screening tests. The current TEFs used to estimate the risk of DLCs in food are primarily based on \textit{in vivo} information from rat and mouse experiments. Our CTFs, based on human cell responses, show clear differences compared to the current TEFs. For instance, the CTF of 23478-PeCDF is as high as the CTF for 2378-TCDD, and the CTF of PCB 126 is 30 times lower than the corresponding TEF. Both of these DLCs are common congeners in fish in the Baltic Sea. Due to the severe effects of DLCs and their impact on environmental and human health, it is crucial to determine if other compounds have similar effects. To find such compounds, we developed a virtual screening protocol and applied it to a set of 6,445 industrial chemicals. This protocol included a presumed 3D representation of AhR and the structural and chemical properties of known AhR ligands. This screening resulted in a priority list of 28 chemicals that we identified as potential AhR ligands.

Keywords
dioxin-like compounds, multivariate analysis, toxic equivalency factor, quantitative structure-activity relationship, descriptors, virtual screening, \textit{in vitro}, species variation, aryl hydrocarbon receptor