

EVALUATION OF THE ESTROGENIC EFFECT OF POLYCHLORINATED BIPHENYLS WITH REGARD TO THEIR METABOLIC ACTIVATION BY APPLICATION OF *IN SILICO* TECHNOLOGIES

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Abstract

Hydroxylated polychlorinated biphenyls (OH-PCBs) major metabolites of PCBs, have been reported to present affinity to the estrogen receptor and induce receptor-mediated responses. The early identification of PCBs which may act as estrogen binders was investigated by making use of computational tools for chemical risk assessment. As an area of growing concern a strategy for development of such tools is one of the primary tasks of governmental and international organizations. In the current study the estrogenic potential of several PCBs is analyzed by using widely accepted and standardized computational program. The obtained results suggest that the system is equipped with scientific reliable modules for prediction of the estrogenic potential of diverse chemicals as well as robust machinery for adequate metabolism simulation.

Toxic effects of PCBs

Polychlorinated biphenyls (PCBs) are widespread contaminants that were used as heat transfer fluids, hydraulic fluids, solvent extenders, plasticizers, etc. PCBs are highly lipophilic and accumulate in the liver. A large number of studies have reported that some PCB mixtures possess diverse toxic effects including reproductive toxicity. Hydroxylated PCBs (OH-PCBs), a major biological metabolite group of PCBs, are formed by the cytochrome P-450 monooxygenase enzyme systems in humans and wildlife. While many of these OH-PCBs are further conjugated with glucuronic acid, glutathione, or sulfate, which facilitates their excretion, some OH-PCBs persist in the body which allow them to exert different toxic effects.

QSAR Toolbox

The OECD QSAR Toolbox [OECD] is designed around the workflow a regulator/researcher would typically follow. The first step is to identify the chemical of interest, and the Toolbox allows standard options for chemicals input (SMILES, CAS, ECI code). When the chemical is entered it is possible to retrieve all available toxic data from the largest publicly available endpoint datasets incorporated in the system. The system is equipped with profilers for identification of chemicals that could act as toxicants. The main advantage of the system is the opportunity to investigate a chemical with account to its metabolic fate. It is well known that the chemical in its parent form may not exert toxic effect however after metabolism a reactive metabolite can be produced which may damage biological macromolecules.

Results

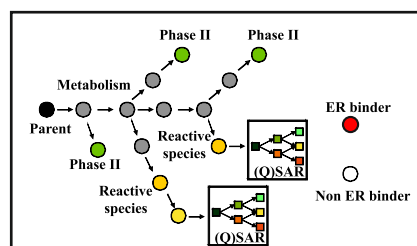
The estrogenic effect of a series of PCB's was analysed by making use of both - profiler for estrogen binding and metabolism simulator incorporated in the QSAR Toolbox.

ER binding profiler

The incorporated ER binding profiling scheme is based on structural and parametric rules extracted from literature sources and supported by experimental data. The ER-binding profiler classifies chemicals as non binders or binders depending on molecular weight (MW) and structural characteristics of the chemicals.

Metabolism simulation

The *in vitro* rat liver metabolic simulator represents electronically designed set of biotransformation reactions. The principal applicability of this simulator is associated with the reproduction as well as the prediction of the metabolic activation reactions and pathways of xenobiotic chemicals, which may elicit diverse array of *in vitro* biological effects.



General scheme for ER binding prediction of chemicals with account for their metabolic activation

Investigated PCB's classes

Monosubstitued PCBs	pREC ₂₀	Predicted ER binding effect	Simulated Metabolism
2-Chlorobiphenyl	N/A	Negative	N/A
2-Chlorobiphenyl-4-ol	7.36	Positive	+
5-Chlorobiphenyl	N/A	Negative	N/A
5-Chlorobiphenyl-2-ol	5.31	Positive	+

Dichlorobiphenyls			
2',3'-Dichlorobiphenyl	N/A	Negative	N/A
2',3'-Dichlorobiphenyl-2-ol	5.47	Positive	+
2',5'-Dichlorobiphenyl	N/A	Negative	N/A
2',5'-Dichlorobiphenyl-2-ol	5.38	N/A	-
3',4'-Dichlorobiphenyl	N/A	Negative	N/A
3',4'-Dichlorobiphenyl-2-ol	5.28	Positive	+

Trichlorobiphenyls	pREC ₂₀	Predicted ER binding effect	Simulated Metabolism
2,2',5'-Dichlorobiphenyl	N/A	Negative	N/A
2,2',5'-Dichlorobiphenyl-3-ol	6.40	Positive	+
2',3,3'-Trichlorobiphenyl	N/A	Negative	N/A
2',3,3'-Trichlorobiphenyl-2-ol	5.39	N/A	-

Tetrachlorobiphenyls			
2,2',4',6'-Tetrachlorobiphenyl	N/A	Negative	N/A
2,2',4',6'-Tetrachlorobiphenyl-4-ol	8.89	Positive	+
2',3,4,4'-Tetrachlorobiphenyl	N/A	Negative	N/A
2',3,4,4'-Tetrachlorobiphenyl-2-ol	5.21	Negative	+

Experimental data, simulated metabolism and ER binding prediction results for PCB's used in the current study.

Conclusion

The application of computational tools for chemical risk assessment allows identification of hazardous substances at very early stages of their assessment. The presented application of the platform OECD QSAR Toolbox for identification of hydroxylated polychlorinated biphenyls as estrogen binders encourage further using and refining of such kind of tools for their application in the field of computational (eco)toxicology. It should be pointed out that the virtual screening cannot be considered as tool to find all potentially estrogenic active chemicals from a screening database, nor is it suitable for replacing *in vitro* or *in vivo* testing. However, computational models are valuable tools for prioritizing potential estrogenic compounds for biological evaluation, thereby helping to find a majority of estrogenic compounds already at the beginning of a systematic *in vitro*/*in vivo* screening campaign.