A. Pérez-Garrido, F. Girón-Rodríguez, A. Morales Helguera, F. Borges & R.D. Combes (2013) Topological structural alerts modulations of mammalian cell mutagenicity for halogenated derivatives, SAR and QSAR in Environmental Research, 25:1, 17-33, DOI: 10.1080/1062936X.2013.820791

Abstract

Genotoxicity is a key toxicity endpoint for current regulatory requirements regarding new and existing chemicals. However, genotoxicity testing is time-consuming and costly, and involves the use of laboratory animals. This has motivated the development of computational approaches, designed to predict genotoxicity without the need to conduct laboratory tests. Currently, many existing computational methods, like quantitative structure–activity relationship (QSAR) models, provide limited information about the possible mechanisms involved in mutagenicity or predictions based on structural alerts (SAs) do not take statistical models into account. This paper describes an attempt to address this problem by using the TOPological Substructural MOlecular Design (TOPS-MODE) approach to develop and validate improved QSAR models for predicting the mutagenicity of a range of halogenated derivatives. Our most predictive model has an accuracy of 94.12%, exhibits excellent cross-validation and external set statistics. A reasonable interpretation of the model in term of SAs was achieved by means of bond contributions to activity. The results obtained led to the following conclusions: primary halogenated derivatives are more mutagenic than secondary ones; and substitution of chlorine by bromine increases mutagenicity while polyhalogenation decreases activity. The paper demonstrates the potential of the TOPS-MODE approach in developing QSAR models for identifying structural alerts for mutagenicity, combining high predictivity with relevant mechanistic interpretation.

Keywords: QSAR; TOPS-MODE; mutagenicity; aliphatic halogenated derivatives; genotoxicity; structural alerts