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Octanol-water distribution coefficient (log *D*) as molecular descriptor to count environmental effect in QSAR models: comparison on experimental and predicted values for common reference drug substances for wide pH scale

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Approximately 60% of common chemicals and 80% of therapeutics are in an ionized state within the pH ranges of organisms or the environment. A great simplification is often made in the description of the processes in the organism and the environment, if molecular descriptors corresponding to the neutral forms of the molecules are used to describe them or to predict the corresponding properties. One of such frequently used molecular descriptors is the octanol-water partition coefficient and its logarithm (log P_{ow}), which describes the hydrophobicity-hydrophilicity of neutral compounds. Ideally, one should use molecular descriptors that correspond to the conditions and mechanism of the studied system or property that we want to model.

The ionization of a compound in a molecular descriptor is obviously difficult to handle. A good opportunity for this is provided by the octanol-water distribution coefficient and its logarithm (log *D*). Log *D* is currently only structural property that in simple way allows environmental effects (pH) on the ionization of a chemical compound to be taken into account in QSAR/QSPR models. Experimental measurements of log *D* values are time-consuming, as the values have to be determined at different pH values, and therefore the literature data are often incomplete. Due to the lack of consistent experimental data, log *D* values fitted using calculated log P_{ow} and dissociation constant (pKa) values are used to develop predictive models. The accuracy of such predicted values and fitting parameters is not known and has not been independently verified (validated).

This presentation looks at log *D* as a possible molecular descriptor that takes into account the ionization of compounds and its use in QSAR models. More specifically, experimentally measured pH-log *D* profiles are examined and how well or poorly log *D* calculators predict various parameters of pH-log *D* profiles. Possible bottlenecks that could help improve predictions and enable wider use of log *D* are pointed out.

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