[L6] Computational Toxicology: Alarms about Chemical Alerts

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Structural alerts (often derived by manual SAR analysis of chemical series) have become widely accepted in chemical toxicology and regulatory decision support as simple and transparent means to flag potential chemical hazards and group compounds into categories for read-across. Conversely, statistical QSAR models have found strong, independent application in predicting chemical toxicity, although their practical use, especially for regulatory purposes, has been hampered by the lack of transparency and interpretability in simple structural terms. Historically, these two approaches have been used as independent computational toxicology tools: the former to identify chemical alerts with the emphasis on mechanistic interpretation whereas the latter for quantitative toxicity assessment agnostic of the underlying toxicity mechanisms. We show that single alerts cannot be used universally to predict compound toxicity (or suggest toxicity-reducing chemical modification) in isolation from taking into account concurrent effects of other chemical features present in a compound. We illustrate these findings with molecular modeling studies of endocrine disruption, skin sensitization, and hepatotoxicity. We also illustrate the unreliability of chemical alerts using an example of PAINS (Pan-Assay Interference compoundS) alerts. These alerts are used widely to eliminate unreliable virtual screening hits but our studies show that PAINS alerts have low if any statistical significance and their use should be avoided. We advance a bridging data-analytical strategy that combines chemical alerts and QSAR models for improved prediction accuracy. As part of these strategy, we detect chemical alerts by interpreting QSAR models in terms of statistically significant chemical features, which could generate more reliable alerts than SAR studies. However, we argue that the presence of structural alerts (however derived) in a chemical should be perceived as no more than a research hypotheses rather than reliable assertion of this compound's toxicity. We posit that these hypotheses should be validated or refuted by the respective QSAR models. In summary, we advocate for the synergistic use of chemical alerts and QSAR models for designing novel compounds with the reduced toxicity, which has implications for green chemistry.