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Modifications to Toxtree's Revised Cramer Module in the Context of Cramer Classification Predictions for Medical Device Extractables

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Toxicological risk assessment of medical device extractables often deals with chemicals lacking complete data packages, for which using a threshold of toxicological concern (TTC) approach is warranted. Recent international guidelines (ICH M7, ISO 21726:2019) offer a road map for evaluating such data-poor chemicals, whereby non-mutagenic extractables may be assigned a non-cancer TTC. Along these lines, the Cramer decision tree categorizes chemicals into three different structural classes – Class I, Class II, and Class III – each corresponding to an estimated hazard potential and TTC for systemic toxicity in humans. Previously, we compared Cramer classifications (and corresponding non-cancer TTCs) for 164 chemicals extracted from various medical devices predicted using different modules within the *in silico* prediction tools Toxtree version 3.1.0 ("Cramer rules," "Cramer rules with extensions," and "revised Cramer rules") with expert judgment and identified some systematic errors in the way Toxtree applied the "revised Cramer rules" module for aliphatic alcohols, aldehydes, ketones, carboxylic acids, amines, amides, and polyethylene glycols. In this study, we aim to correct some of these systematic errors by making modifications to rules Q16 and Q18. More specifically, we modified the way Toxtree interprets the structures of polyethylene glycols, amides, acrylic acid, and methacrylic acid. These modifications resulted in a significant improvement in the concordance of the modified module with our expert judgement for acyclic compounds – compared with the 51.4% concordance shown by "revised Cramer rules," the modified module showed 75.2% concordance. Our findings support the idea that addressing some of the systematic errors exhibited by Toxtree's "revised Cramer rules" module significantly improves its performance, reducing the need for the application of expert judgement. The ultimate goal of addressing these systematic errors is to completely eliminate the need for expert judgement when assigning Cramer classifications to acyclic compounds.