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Evaluating the Suitability of Three Types of Cramer Decision Trees for Predicting the Toxicity of Medical Device Constituents

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Background and Purpose: The Cramer decision tree by Cramer *et al.* (1978) was used to prepare tiered non-cancer thresholds of toxicological concern (TTCs) (Munro *et al.,* 1996; Kroes *et al.*, 2004). TTCs are exposure levels with negligible toxicological risk that have broad acceptance across regulatory authorities, as indicated by the recommended use of Cramer Class TTC values in the International Organization for Standardization (ISO) Technical Specification (TS) 21726:2019 (ISO, 2019). The Cramer classification system evaluates chemical structures to characterize potential toxicological harm according to three groups: Class I chemicals with simple structures, efficient metabolic pathways, and low potential toxicities; Class II chemicals with structures that are less innocuous than Class I but do not contain structural features suggestive of toxicity; and Class III chemicals with structural features that may suggest significant toxicity. The applicability of the Cramer classification system to evaluate medical device (MD) constituents identified by the MD TTC project (Builee *et al*., 2024) is assessed using the following *in silico* tools: two ToxTree module (v. 3.1.0) decision trees – the Revised Cramer (RC) and Kroes TTC (Kroes TTC) – and the Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Toolbox Cramer profiler (TB) (4.5 SP1).

Methods: Simplified Molecular-Input Line Entry (SMILES) codes from non-genotoxic constituents identified as part of the MD TTC database (n = 1,527) were batch processed in ToxTree (v 3.1.0) using the RC, Kroes TTC, and TB (4.5 SP1). The results were recorded as Class I, II, or III. No daily input value was provided as part of the Kroes TTC for any chemical. Additionally, expert judgment (EJ) using the three decision trees was applied manually to evaluate accuracy of the automated read-outs. EJ assessed a subset of the constituents (n = 130) bearing a 180-day and/or 2-year repeated dose no observed adverse effect level (NOAEL) provided by the MD TTC database. Concordance between Cramer classification results was evaluated as a percentage. EJ recorded errors due to batch-processed predictions. NOAELs were reviewed by Cramer Class and compared to the historical values of Cramer et al. (1978) to determine the adequacy of the chemical stratification system to predict associated toxicity.

Results: Cramer classifications were assigned to MD constituents using three types of decision tools. Concordance in predictions was highest (65-75% alignment) between the batch-processed RC and TB, and lowest (45-55%) with the Kroes TTC. Higher discordance was observed with the Kroes TTC, possibly because the systematic logic requires input of a daily intake value, which was not accommodated using the batch-process function. Further, prediction disagreements were explored in the subset of constituents with an available long-term NOAEL.

For the subset (n = 130) of constituents having long-term NOAELs, predictions of the TB and RC aligned with experimental toxicity values. For these two tools, the in silico processed predictions tended to assign higher class levels as compared to the EJ conclusion. The Kroes TTC had high discordance (>50%) when compared to any other system. For chemicals with discrepancies between the Kroes TTC and one or more of the various rule-based systems, the Kroes TTC class assignment was generally lower. There

were differentiated NOAEL ranges for Class I and Class III compounds that resemble the reference values from Cramer and Munro (Cramer et al., 1978; Munro et al., 1996); however, due to low sample size, no such analysis was performed for Class II compounds.

Conclusions: An evaluation of free, rule-based QSAR methods for the prediction of Cramer classifications is presented for a large dataset of MD constituents. The results provide evidence of high variability in batch-processed QSAR outputs performed without manual judgment. Concordance was highest between manually applied EJ and the batch-processed RC. When the NOAELs were evaluated using EJ of chemical toxicity, the NOAEL ranges were characteristic of the expected Cramer toxicity levels.

Builee, T; Parker, S; Prabhakar, B; Hsia, FK; Stornetta, A; Bond, SM; Peterson, MK; Levelut, V. 2024. "Derivation of Fit-for-Purpose Non-Cancer Duration-Based TTC Values for Medical Device Constituents." Abstract/Poster #: 3358/P483. Presented at the Society of Toxicology (SOT) 63rd Annual Meeting and ToxExpo, Salt Lake City, UT, March 10-14.

Cramer, GM; Ford, RA; Hall, RL. 1978. "Estimation of toxic hazard - A decision tree approach." *Food Cosmet. Toxicol*. 16(3):255-276.

International Organization for Standardization (ISO). 2019. "Biological evaluation of medical devices - Application of the threshold of toxicological concern (TTC) for assessing biocompatibility of medical device constituents." ISO/TS 21726:2019(E), 12p.

Kroes, R; Renwick, AG; Cheeseman, M; Kleiner, J; Mangelsdorf, I; Piersma, A; Schilter, B; Schlatter, J; van Schothorst, F; Vos, JG; Wurtzen, G. 2004. "Structure-based thresholds of toxicological concern (TTC): Guidance for application to substances present at low levels in the diet." *Food Chem. Toxicol.* 42(1):65-83. doi: 10.1016/j.fct.2003.08.006.

Munro, IC; Ford, RA; Kennepohl, E; Sprenger, JG. 1996. "Correlation of structural class with no-observed-effect levels: A proposal for establishing a threshold of concern." *Food Chem. Toxicol.* 34(9):829-867. doi: 10.1016/S0278-6915(96)00049-X.