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Comparison of Cramer classification between Toxtree, the OECD QSAR Toolbox and expert judgment

Sneha Bhatia [a], Terry Schultz [b], David Roberts [c], Jie Shen [a], Lambros Kromidas [a,*], Anne Marie Api [a]

[a] Research Institute for Fragrance Materials, Inc., 50 Tice Blvd., Woodcliff Lake, NJ 07677, USA
[b] The University of Tennessee, College of Veterinary, 2407 River Dr., Knoxville, TN 37996, USA
[c] Liverpool John Moores University, Liverpool L3 3AF, UK

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ABSTRACT

The Threshold of Toxicological Concern (TTC) is a pragmatic approach in risk assessment. In the absence of data, it sets up levels of human exposure that are considered to have no appreciable risk to human health. The Cramer decision tree is used extensively to determine these exposure thresholds by categorizing non-carcinogenic chemicals into three different structural classes. Therefore, assigning an accurate Cramer class to a material is a crucial step to preserve the integrity of the risk assessment. In this study the Cramer class of over 1000 fragrance materials across diverse chemical classes were determined by using Toxtree (TT), the OECD QSAR Toolbox (TB), and expert judgment. Disconcordance was observed between TT and the TB. A total of 165 materials (16%) showed different results from the two programs. The overall concordance for Cramer classification between TT and expert judgment is 83%, while the concordance between the TB and expert judgment is 77%. Amines, lactones and heterocycles have the lowest percent agreement with expert judgment for TT and the TB. For amines, the expert judgment agreement is 45% for TT and 55% for the TB. For heterocycles, the expert judgment agreement is 55% for TT and the TB. For lactones, the expert judgment agreement is 56% for TT and 50% for the TB. Additional analyses were conducted to determine the concordance within various chemical classes. Critical checkpoints in the decision tree are identified. Strategies and guidance on determining the Cramer class for various chemical classes are discussed.

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1. Introduction

Risk assessment is a scientific process that characterizes the magnitude of risk that chemicals or biologics pose to human and environmental health. Conventionally, risk assessment factors for most human health endpoints are derived from animal studies. The shift towards application of alternative methods has encouraged and enabled risk assessors to incorporate non-animal approaches such as *in vitro* studies and *in silico* methods. Another approach is the Threshold of Toxicological Concern (TTC) concept that may be applied to evaluate materials for their potential toxicity when exposure is very low.

The TTC, as an approach to risk assessment, includes the application of a judicious assurance of safety in the absence of chemical-specific toxicity data. Specifically, there may be no significant risk to human health when exposure is below a threshold level. This approach is based on the Threshold of Regulation (Hattan and Rulis, 1986), which was later expanded to consider the chemical structure in conjunction with toxicity data (Munro, 1990; Munro et al., 1996; Kroes et al., 2004). These analyses focused on systemic exposure following oral administration. The TTC approach was originally developed to address human carcinogenicity and systemic toxicity endpoints. It has a relatively long history of use in the evaluation of food contact chemicals and indirect additives, flavors and contaminants in foods, and impurities in pharmaceuticals (WHO, 2002). Recently, the TTC approach was extended to the safety evaluation of topically applied cosmetic ingredients, including fragrance materials (Blackburn et al., 2005; Kroes et al., 2007). The European Food Safety Authority (EFSA) uses the TTC approach for evaluation of flavors and evaluation of pesticide metabolites in groundwater (EFSA, 2012). Additionally, three independent non-food committees (SCCP, SCHER and SCHENIHR) evaluated

Abbreviations: RIFM, Research Institute for Fragrance Materials, Inc.; TTC, Threshold of Toxicological Concern; TT, Toxtree; TB, OECD QSAR Toolbox; SCCS, Scientific Committee on Consumer Safety; SCHER, Scientific Committee on Health and Environmental Risks; SCENIHR, Scientific Committee on Emerging and Newly Identified Health Risks.

* Corresponding author.
E-mail address: lkromidas@rifm.org (L. Kromidas).

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the potential applications of the TTC and concluded that the TTC approach is scientifically acceptable for human health risk assessment of systemic toxic effects caused by chemicals present at very low levels of exposure. Furthermore, for cosmetics the TTC approach can be used for those compounds which belong to a sufficiently represented structural class in the TTC database and where appropriate exposure data are available (SCHER/SCCS/SCENIHR, 2012). It is important to note that the TTC approach does not apply to proteins, metals, inorganic substances, high molecular weight substances (e.g., polymers), nanomaterials and radioactive substances. Furthermore, polyhalogenated dioxins/dibenzo furans and dioxin-like polyhalogenated biphenyls are excluded. Finally highly potent genotoxic carcinogens and materials that show evidence for high potency are excluded from the TTC approach (EFSA, 2012).

The Cramer decision tree (Cramer et al., 1978) is used for categorizing non carcinogenic chemicals in order to determine their TTC level (Munro et al., 1996; Kroes et al., 2004). The original Cramer decision tree consists of 33 'yes' (Y) or 'no' (N) questions or rules (Q) (see Appendix I). The answer to each question leads to another question until a final Cramer classification for the chemical of interest is established (Cramer et al., 1978). The Cramer decision tree classifies materials into one of three classes (I – low, II – intermediate and III – high). In 2009, a plug-in called "Cramer rules with extensions" was introduced. This plug-in included five extra questions (i.e., 40–44; please note there are no questions 34–39) and an expanded list of natural body constituents for answering Q1. Of all the Cramer rules, Q1 and Q22 are essentially look-up lists. All the other rules are structure-based except rules Q16 and 17 which are only partly structure-based, as they require reference to the literature or searching databases.

Once the Cramer class is determined, a corresponding TTC threshold for non-genotoxicity endpoint is chosen and compared with the exposure to determine whether the material is above or below the TTC threshold. Therefore, assigning the appropriate Cramer class to a chemical that lacks toxicity data is a crucial step to ensure the integrity of its risk assessment. Usually, freely available *in silico* programs, such as Toxtree and the QSAR Toolbox (TB) are used to determine Cramer class. Toxtree is an open source freely available software that was commissioned for development by the European Commission Joint Research Centre's European Chemicals Bureau (ECB) solely for the purpose of determining Cramer classification of chemicals (http://toxtree.sourceforge.net/). Later versions of Toxtree included additional schemes such as the BfR/SICRET skin irritation and corrosion rules and Verhaar scheme. OECD QSAR Toolbox (http://www.qsartoolbox.org/) was commissioned for development by the Organization for Economic Co-operation and Development (OECD). The Cramer classification scheme was included as a module. Although TT and the TB were developed based on the same Cramer decision tree (Cramer et al., 1978), the interpretation of each rule in the two *in silico* programs may vary. Hence, some discrepancies in Cramer classifications by *in silico* programs have been observed. These discrepancies could be due to technical problems such as bugs or interpretation of the rules (Lapenna and Worth, 2011; Patlewicz et al., 2008). Cramer classification discrepancies may lead to unnecessary testing or may cause incorrect waiving of testing. Therefore, it is important to obtain insight into the potential problems of any *in silico* programs that may lead to discrepancies in the Cramer classification.

In this work, we evaluated 1016 fragrance materials by conducting Cramer classification using Toxtree, OECD QSAR Toolbox and expert judgment. We highlighted discrepancies in Cramer classification with certain chemical classes due to differences in the interpretation of the Cramer questions. We also outlined key strengths and weaknesses of each *in silico* program. We also present strategies to further refine the Cramer questions within the *in silico* programs, to reduce ambiguity and improve concordance with human expert assignments. (expert judgment). In this work, our experts determined Cramer classes by using the original Cramer rules (i.e., without extensions, as shown in Cramer et al., 1978). Hence, programs with the extensions are not discussed in our current work.

2. Methodology

2.1. Data set of fragrance materials

A total of 1016 fragrance ingredients from diverse generic chemical classes (i.e.: acetals, alcohols, aliphatic aldehydes, aromatic aldehydes, amines, carboxylic acids, esters, ethers, heterocyclics, hydrocarbons, ionones, ketones, lactones, phenols, and sulfur containing fragrance materials) were selected. These 1016 ingredients were low molecular weight organic chemicals and did not include any of the exclusions that are not covered by the TTC approach. Materials in each chemical class were categorized by expert assessment into several subclasses. The categorization of these materials followed the principles as outlined in the ECHA technical guidance and OECD guidance on grouping (OECD, 2014; ECHA, 2008). Briefly, materials were clustered together with similar chemical structure/functional groups, similar reactivity, similar metabolism and similar physicochemical properties (Belsito et al., 2011a,b,c, 2012, 2013a,b).

2.2. Determination of Cramer classification

The chemical structures of these 1016 fragrance materials were represented using the simplified molecular-input line-entry system (SMILES) (Weininger, 1988). The SMILES were used as input for Toxtree (TT), Version 2.6.0 and the OECD QSAR Toolbox (TB), Version 3.1. The Cramer class of each material was determined by the Cramer rule decision tree feature in TT and toxic hazard classification by Cramer (original) feature in TB. The path information of the Cramer class from these programs was also generated. In addition, these 1016 materials were manually classified by experts into different Cramer classes based on the original Cramer rules (Cramer et al., 1978). A quality control process was conducted to verify the manual classification by assigning some materials to two independent experts in a blind manner.

2.3. Concordance analysis of in silico programs with expert judgment

As mentioned above, all of the 1016 materials had a Cramer class assigned by TT, TB and expert judgment. The overall concordances of 1016 materials were calculated between TT vs the TB, TT vs expert judgment, and the TB vs expert judgment.

Further, the concordances of each chemical class between the two *in silico* programs and expert judgment were calculated to identify those chemical classes with potential discrepancy issues. For deeper insight, the subclass concordances of each subclass in those three chemical classes with the lowest concordance, between *in silico* programs and expert judgment, were also calculated.

3. Results

3.1. Overall concordance

The Cramer modules in TT and TB were developed based on the same Cramer decision tree (i.e., rules). The interpretation of each rule in the two *in silico* programs may vary. For example – ethyl 2-tert-butyl-cyclohexyl carbonate is assigned as Class III by the TB

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