Utility of Computational Toxicology at FDA Center for Tobacco Products in Evaluation of Potential Hazards Due to Ingredients in Tobacco Products

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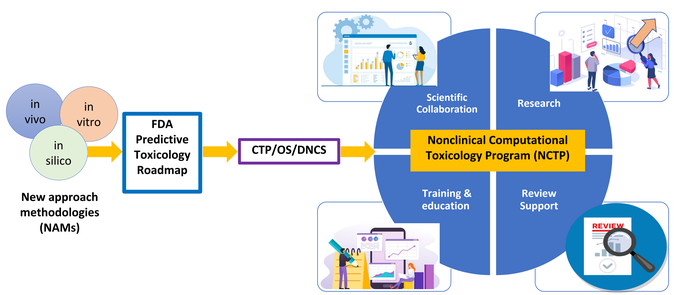
Abstract

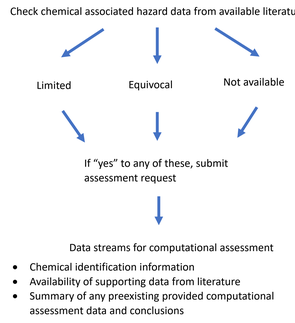
FDA's Predictive Toxicology Roadmap outlines key strategies by which new approach methodologies (NAMs), including computational toxicology methods, help shift from animal-derived toxicity results to reliable predictive models that evaluate toxicant hazard characterizations. Computational toxicology offers great promise for supporting hazard assessments of chemicals when associated toxicological data is limited, equivocal or absent. Within the Division of Nonclinical Science (DNCS), Office of Science (OS), Center for Tobacco Products (CTP), the Nonclinical Computational Toxicology Program (NCTP) conducts and translates computational toxicology assessments to evaluate their future role and utility in the toxicology review of new tobacco products. The NCTP seeks to advance regulatory science of tobacco products by including computational toxicology tools, training, and research in the synthesis of evidence regarding respiratory, mutagenic, genotoxic, and carcinogenic hazards associated with ingredients and constituents. The need for computational assessment of tobacco-associated chemicals is based on the scientific assessment of a given chemical's hazard data or any associated information submitted in a tobacco product application. Computational toxicology models are under constant evaluation for their reliability and validity by NCTP. These methods assist the triage of chemicals towards translation to toxicology assessment with the support of expert judgment. Each computational prediction is evaluated by NCTP using raw computational outputs, supporting data from models, and associated empirical data to make an overall data call or to evaluate submitted data calls. The applied use of computational toxicology tools in DNCS demonstrates that these approaches are useful for identifying potential hazards associated with chemical constituents in tobacco products. Based on applied-use scenarios, NCTP developed frameworks and workflows for triaging chemicals for computational assessment, evaluating and interpreting predictions, and recording and reporting data summaries. Strategies are under development to ensure validation and improve predictivity of applied computational toxicology models and to construct fit-for-purpose training datasets to achieve improved tobacco hazard assessments. DNCS engages in computational toxicology to provide innovative, reliable, and efficient NAMs to support traditional toxicology hazard assessments in the regulatory environment. NCTP aspires to bring data-driven computational approaches to the forefront, augmenting the quality and efficiency of the toxicological assessment of tobacco product associated hazards.

NCTP Mission Concept

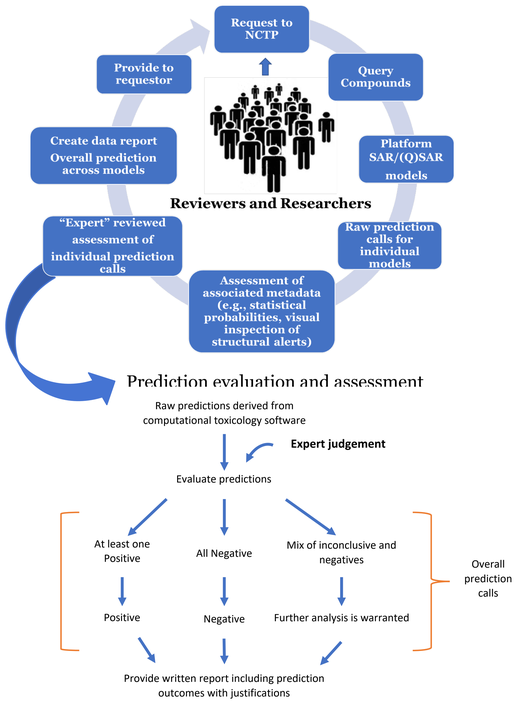


NCTP workflow and design

Step 1: Criteria for internal computational assessment

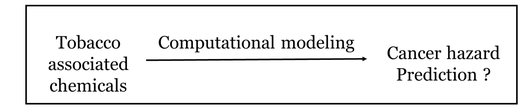


Step 2: Evaluate computational assessment request according to NCTP Internal Workflow

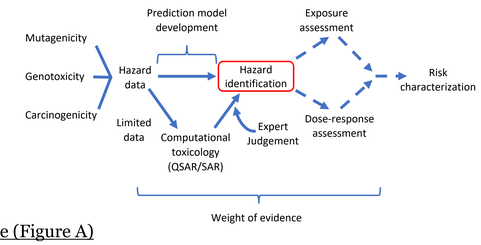


Expert (human) interpretation is incorporated into the evaluation of computational derived predictions

Pilot – Cancer hazard classification



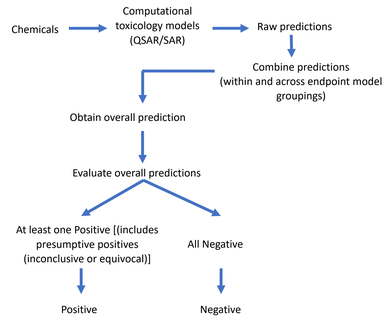
A



Rationale (Figure A)

- The determination of cancer hazard and risk in humans is evaluated based on a weight of evidence approach comprising mechanisms of action including pathways driven by genotoxic, non-genotoxic (such as metabolic), and/or mutagenic potential.
- Computational toxicology models can support identification of probable chemical hazards when experimental data is limited or absent

B

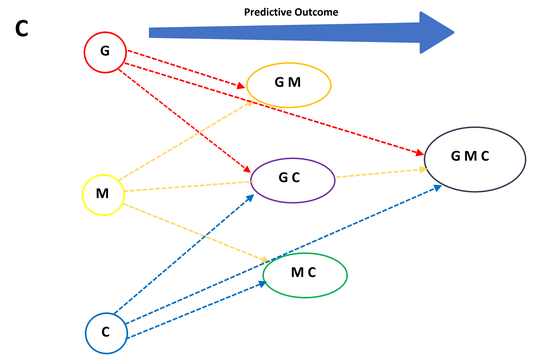


Design (Figure B)

- A total of 102 chemicals associated with tobacco products were analyzed by selected commercially available computational toxicology software
- For each chemical, computerized model predictions based on statistical and decision based models for mutagenicity, genotoxicity, and carcinogenicity assays were obtained using default settings
- Combinations of these model predictions were applied to derive an overall cancer outcome for each chemical using a conservative approach to minimize false negatives
- The predicted cancer outcomes were compared to established and proposed HPHC cancer designations to assess the predictive performance of the computational approach

Hypothetical framework of model combinations (Figure C)

C



Computational model derived predictions for genotoxicity (G; red), mutagenicity (M; yellow), and carcinogenicity (C; blue) endpoint groupings were assessed in combinations as shown here. Increasing sizes of the circles indicate that predictive outcomes should improve as an increasing number of model-derived outcome predictions are evaluated using a conservative approach.

Abbreviations:
HPHC: harmful and potentially harmful constituents
(Q)SAR: (quantitative) structure-activity relationship
SAR: structure-activity relationship

This pilot is a hypothetical exercise and is not considered a methods validation or an endorsement of any modeling product

Summary and Perspectives

- FDA encourages the consideration of NAMs as supportive data streams when toxicological data are limited or absent. The NCTP has been formed to explore this approach within DNCS.
- A pilot using commercial (Q)SAR software platforms was performed using mutagenicity, genotoxicity, and carcinogenicity pathway-driven models to predict cancer hazard for 102 tobacco-associated chemicals. A conservative approach combining these pathway-driven models improves the prediction of cancer designation for tobacco-associated chemicals when compared to single model predictions.
- Within the framework of the Predictive Toxicology Roadmap, NCTP aims to develop computational approaches to support tobacco product review and applied research. Further exploration of (Q)SAR methodology is warranted to determine the endpoint(s) and computational approach(es) best suited to hazard identification for tobacco product chemicals.

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