Alexander Blanchette, Ph.D.,

Health Scientist

Summary of Experience

Dr. Alexander Blanchette is a toxicologist specializing in the use of computational methods and other new-approach methods (NAMs) to aid in all phases of risk assessment, with broad experience in using the R programming language. He received his Bachelor of Science in Forensic Chemistry from Western New England University where he worked to develop an alternate and improved field test for marijuana. After receiving his undergraduate degree, he joined the Toxicology Ph.D. program at the University of Maryland Baltimore and after a year, he transferred to Texas A&M, where he received his Ph.D. in Toxicology as a member of Dr. Weihsueh Chiu's lab. Here, he developed his computational toxicology skillset, which extends to other aspects of risk assessment, including in Bayesian concentration-response modeling, vitro – to–in vivo extrapolation, integration of multiple streams of data to solve toxicological problems, meta-analysis and meta-regression, and the application of machine learning techniques in toxicology, including machine-aided literature selection. Dr. Blanchette served in a prominent technical and communication role in the development, testing, and acceptance of a new integrated computational method for deriving Toxic Equivalency factors for Dioxin-like compounds, which integrated Bayesian concentration response, machine learning, and meta-analysis techniques to integrate diverse and heterogeneous data sets. He also has experience conducting a wide array of statistical analyses, such as ANOVA, mixed-effects modeling, and T-tests, and creating clear and compelling visualizations in R, Graphpad Prism, Microsoft Excel, and ToxPi. His toxicological skill set includes general toxicology, systematic literature review across a broad range of subjects, and in-depth knowledge of tools and datasets that can be leveraged to solve even the most complicated toxicological problems.

Education

Bachelor of Sciences (B.S.), Forensic Chemistry, 2016, Western New England University

Doctor of Philosophy (Ph.D.), Toxicology, 2021, Texas A&M University

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Project Experience

Computational Toxicology

Developed and applied a computational workflow utilizing data from induced pluripotent stem cell-derived cardiomyocytes to derive measurements of hazard and risk, taking population variability into account. This workflow was utilized to screen more than 1000 environmental chemicals, pharmaceuticals, and other compounds of interest for potential cardiotoxic risk for the "average" individual and the more sensitive individuals. This work yielded 5 publications, 3 of which were first author publications, while the rest were second author publications.

Played a key role in the development, application, and communication of a complex and multifaceted computational workflow for the derivation of toxic equivalency factors (TEFs) for dioxin-like compounds (DLCs). This workflow utilized Bayesian concentration-response modeling, machine learning, and Bayesian meta-analysis to integrate large amounts of highly varied toxicological data with different units, experimental models, endpoints, and more to predict DLC toxicity, accounting for uncertainty at each step of the workflow. This work has worldwide implications and has been reviewed and accepted by the World Health Organization (WHO) as the method to derive TEFs and has yielded 2 academic publications (second author).

Developed a highly accurate machine learning model (accuracy 90+%) for predicting inhalation portal of entry (POE) toxicity for compounds of interest using publicly available data. As part of this effort, he was a major contributor to the expert judgement assignment of POE toxicity calls using *in vivo* data and the primary contributor to efforts related to the development of the computational workflow: data collection, wrangling, and preparation; training set development; and model training, testing, and validation.

Developed a Bayesian dose-tissue concentration (D-TC) model for deriving the tissue-specific relative bioavailability (RBA) values for manganese as a part of electric arc furnace slag using *in vivo* experimental data. This method represented a major improvement over the former frequentist linear regression method and allowed for the derivation of RBA values from dose-tissue concentration data that would not allow for it using traditional methods. This method was employed in a published risk assessment (second author) of metals in slag where the Bayesian D-TC model was used to generate a critical input for a probabilistic risk assessment, which itself fed into a physiologically based pharmacokinetic model (see Pharmacokinetic Modeling section). As part of this work, key contributions were made to the original relative bioavailability study, which itself was published (third author).

Pharmacokinetic Modeling

Modified, updated, and applied a previously developed pharmacokinetic model for evaluating Mn in a receptor across life stages, including during fetal development stages where both the mother and the fetus are accounted for. This model was specifically applied to develop an acute 24-hour health-based inhalation guideline for manganese and published in a peer reviewed journal (second author)

Adapted and applied a previously published manganese pharmacokinetic model for additional exposure scenarios as part of a larger Risk Assessment of Electron Arc Furnace Slag. This included significant changes to model code, creation of input data files, and interpretation and visualization of output data from the model. This effort also included the development and

implementation of a Bayesian model for the derivation of manganese relative bioavailability values and is in production to be published in a peer-reviewed journal.

Key contributor to the review of proposed health-based values for PFAS compounds which included a significant pharmacokinetic portion. The pharmacokinetic model was thoroughly reviewed and evaluated with sensitivity analyses and other tests of its function and biological applicability. Provided comments as part of the public commenting period on the proposed values.

Data Analysis and Statistics

Experienced in leveraging historical control data and its use in evaluating the significance of dose-related effects in compounds of interest. Included in this is experience in evaluating the veracity of historical control data, including verifying its consistency, identifying any trends that may be present, and quality assurance. This expertise has been leveraged in a peer-reviewed publication (seventh author).

Highly experienced in leveraging an array of tools including R, Biorender, and ToxPi to create clear, compelling, and highly informative visualizations. Every authorship has included the generation of at least one visualization that was included in the publication.

Expertise in the utilization of high-throughput hazard data resources (ToxCast, Tox21) to aid in addressing a variety of toxicological problems. This includes maintaining a locally hosted copy of the ToxCast database and performing targeted and nontargeted searches for applicable data and performing data curation to ensure the presence or absence of activity in identified assays.

Professional Experience

Scientist III, ToxStrategies, LLC, August 2021 – November 2023

Experience serving a diverse set of clients, including in the animal feed industry, human foods clients, oil and gas, as a government subcontractor to support EPA's Endocrine Disruptor Screening Program, and more. Key contributor to development, application, and advocation of a novel computational method that has been adopted by the Word Health Organization for the derivation of updated Toxicity Equivalency Factors for dioxin-like compounds (see *Publications* section below). Lead an effort in the Health practice to standardizing Coding and Computational practices and served as the leader of the Quantitative Methods internal group for sharing and learning about different methods used for projects around the firm.

Graduate Research Assistant, Weihsueh Chiu Lab – Texas A&M University, August 2017 – June 2021

Gained extensive computational toxicology experience through the utilization of the Stan platform integrated into R to conduct Bayesian concentration-response analyses of *in vitro* data collected from induced pluripotent stem cell derived cardiomyocytes. This approach's goal was to screen hundreds of environmental and pharmaceutical compounds for potential cardiotoxic effects across the population. As part of this, there were significant contributions made to develop and validate this new *in vitro-in silico* new approach method for hazard assessment, population variability quantitation, and risk assessment. This includes utilizing exposure data and the httk package in R to conduct high throughput in silico toxicokinetic analyses.

Professional Membership and Service

- Society of Toxicology (SOT)

  Member of Regulatory and Safety Evaluation, Biological Modelling, Computational Toxicology specialty sections as well as the North Carolina regional chapter

Peer-Reviewed Publications

Thompson, C.M., G. Broby, Z. Keig-Shevlin, R. Smith, A. Franzen, K. Ulrich, A.D. Blanchette, and C. Doepker. Assessment of the in vivo genotoxic potential of three smoke flavoring primary product mixtures. Environ Mol Mutagen. In Production. doi: 10.1002/em.22576

Perry, C.S., A.D. Blanchette, S.N. Vivanco, A.H. Verwiel, and D.M. Proctor. 2023. Use of physiologically based pharmacokinetic modeling to support development of an acute (24-hour) health-based inhalation guideline for manganese. Regul Toxicol Pharmacol. Oct 19;145:105518. doi: 10.1016/j.yrtph.2023.105518. Epub ahead of print. PMID: 37863417.

Ring, C., A. Blanchette, W.D. Klaren, S. Fitch, L. Haws, M.W. Wheeler, M. DeVito, N. Walker, and D. Wikoff. 2023. A multi-tiered hierarchical Bayesian approach to derive toxic equivalency factors for dioxin-like compounds. Regul Toxicol Pharmacol. Sep;143:105464. doi: 10.1016/j.yrtph.2023.105464. Epub 2023 Jul 27. PMID: 37516304

Proctor, D.M., S.N. Vivanco, and A.D. Blanchette. 2023. Manganese relative oral bioavailability in electric arc furnace steel slag is influenced by high iron content and low bioaccessibility. Toxicol Sci. 193(2): 234–243. doi: 10.1093/toxsci/kfad037. PMID: 37074943

Blanchette, A.D., S.D. Burnett, I. Rusyn, and W.A. Chiu. 2022. A tiered approach to population-based in vitro testing for cardiotoxicity: Balancing estimates of potency and variability. J Pharmacol Toxicol Methods. Mar-Apr;114:107154. doi: 10.1016/j.vascn.2022.107154. Epub 2022 Jan 6. PMID: 34999233

Burnett, S.D., A.D. Blanchette, W.A. Chiu, and I. Rusyn. 2021. Cardiotoxicity Hazard and Risk Characterization of ToxCast Chemicals Using Human Induced Pluripotent Stem Cell-Derived Cardiomyocytes from Multiple Donors. Chemical Research in Toxicology. Sep 20;34(9):2110-2124. doi: 10.1021/acs.chemrestox.1c00203. Epub 2021 Aug 27. PMID: 34448577

Luo, Y.S., Z. Chen, A.D. Blanchette, Y.H. Zhou, F.A. Wright, E.S. Baker ES, W.A. Chiu, and I. Rusyn. 2021. Relationships between coinstituents of energy drinks and beating parameters in human induced pluripotent stem cell (iPSC) cardiomyocytes. Food and Chemical Toxicology. 149. doi: 10.1016/j.fct.2021.111979. PMID: 33450301

Blanchette, A.D., S.D. Burnett, F.A. Grimm, I. Rusyn, and W.A. Chiu. 2020. A Bayesian Method for Population-wide Cardiotoxicity Hazard and Risk Characterization using an In Vitro Human Model. Toxicological Sciences. 178(2):391-403. doi: 10.1093/toxsci/kfaa151. PMID: 33078833.

Burnett, S.D., A.D. Blanchette, F.A. Grimm, J.S. House, D.M. Reif, F.A. Wright, W.A. Chiu, and I. Rusyn. 2019. Population-based toxicity screening in human induced pluripotent stem cell-derived cardiomyocytes. Toxicology and Applied Pharmacology. 381:114711. doi: 10.1016/j.taap.2019.114711. PMID: 31425687

Blanchette, A.D., F.A. Grimm, C. Dalaijamts, N.H. Hsieh, K. Ferguson, Y.S. Luo, I. Rusyn, and W.A. Chiu. 2019. Thorough QT/QTc in a Dish: An In Vitro Human Model That Accurately Predicts Clinical Concentration-QTc Relationships. Clinical Pharmacology & Therapeutics. 105(5):1175-86. doi: 10.1002/cpt.1259. PMID: 30346629

Grimm, F.A., A. Blanchette, J.S. House, K. Ferguson, N-H Hsieh, C. Dalaijamts, A.A. Wright, B. Anson, F.A. Wright, W.A. Chiu, and I. Rusyn. 2018. A human population-based organotypic in vitro model for cardiotoxicity screening. ALTEX. 35(4):441-52. Epub 2018/07/08. doi: 10.14573/altex.1805301. PMID: 29999168.

Published Abstracts

Proctor, D., S. Vivanco, and A. Blanchette, A. 2023. Relative Oral Bioavailability of Manganese in Electric Arc Furnace Steel Slag Is Influenced by High Iron Content and Low Bioaccessibility. 2023. Abstract # 4227. Poster Presentation at Society of Toxicology (SOT) Annual Meeting and ToxExpo. March 19-23, 2023. Nashville, TN.

Blanchette, A.D., S. Burnett, F.A. Grimm, I. Rusyn, and W. Chiu. 2021. A Bayesian Method for Population-Wide Cardiotoxicity Hazard and Risk Characterization Using an In Vitro Human Model. Symposium Session # 1175. Oral Symposium session presentation at the 2021 Society of Toxicology (SOT) Annual Meeting. March 12-26.

Blanchette, A.D., S. Burnett, F.A. Grimm, I. Rusyn, and W. Chiu. 2020. An in vitro-in silico model for characterizing hazard and population variability in cardiotoxicity induced by environmental chemicals. 2020. Abstract #2040. Society of Toxicology (SOT) Annual Meeting and ToxExpo (Cancelled due to Covid).

Blanchette, A.D., F.A. Grimm, C. Dalaijamts, N. Hsieh, F. Ferguson, Y. Luo, I. Rusyn, and W. Chiu. 2019. Thorough QT/QTc in a Dish: An In vitro Human Model That Accurately Predicts Clinical Concentration-QTc Relationships. 2019. Abstract #3452. Late-Breaking Poster Presentation at Society of Toxicology Annual Meeting. March 10-14, 2019. Baltimore, MD.

Presentations

Blanchette, A.D., S. Burnett, F.A. Grimm, I. Rusyn, and W. Chiu. 2021. A Bayesian Method for Population-Wide Cardiotoxicity Hazard and Risk Characterization Using an In Vitro Human Model. 2021. Symposium Session # 1175. Oral Symposium session presentation at the Society of Toxicology (SOT) Annual Meeting. March 12-26, 2021.

Blanchette, A.D., S. Burnett, F.A. Grimm, I. Rusyn, and W. Chiu. 2020. A Bayesian New Approach Method for Human Population-wide Risk Characterization of Cardiotoxicity. Texas A&M Toxicology Symposium Series. November 2, 2020.

Blanchette, A.D., S. Burnett, F.A. Grimm, I. Rusyn, and W. Chiu. 2020. An in vitro-in silico model for characterizing hazard and population variability in cardiotoxicity induced by environmental chemicals. Society of Toxicology: Texas Edition. April 4th, 2020

Blanchette, A.D., F.A. Grimm, C. Dalaijamts, N. Hsieh, F. Ferguson, Y. Luo, I. Rusyn, and W. Chiu. 2019. Thorough QT/QTc in a Dish: An In vitro Human Model That Accurately Predicts Clinical Concentration-QTc Relationships. Late-Breaking Poster Presentation at Society of Toxicology Annual Meeting. March 10-14, 2019. Baltimore, MD.

Blanchette, A.D., F.A. Grimm, C. Dalaijamts, N. Hsieh, F. Ferguson, Y. Luo, I. Rusyn, and W. Chiu. 2018. An in vitro Human Bayesian Population Pharmacodynamic Model for Predicting Effects on Heart Rhythm. 2018. Poster Presentation at the EPA Ogranotypic Culture Models STAR center update meeting. May 22, 2018.

Blanchette, A. 2015. The Development of a Solid Phase THC Extraction Method from Whole Blood. Oral Presentation at the North Eastern Association of Forensic Sciences (NEAFS) Annual Meeting. October 15th, 2022.