2023 SOT Annual Meeting & ToxExpo
Session: Computational Toxicology II
Poster: P183
Tuesday, March 21, 2023
9:00am - 10:45am

Framework for *In Silico* Toxicity Screening of Novel Odorants

Isaac Mohar, Ph.D., DABT; Brad C. Hansen; Destiny M. Mims; Joel D. Mainland, Ph.D.

Predicting odor perception from molecular structure is a key challenge in olfaction, but validating current predictive models requires measuring human perception of novel odorants that have not undergone safety testing. Although *in silico* prediction tools are widely applied in chemical risk assessment and risk management, there are currently no transparent *in silico* models to predict inhalation toxicity. We derived toxicology-based maximum recommended solution concentrations for odorant chemicals based on a transparent *in silico* approach, using chemical structure alone to support a psychophysical study of novel odorants in which human volunteers sniffed the headspace of a solution in a vial. Our decision tree was based on well-established open-source decision trees for assessing mutagenicity (rule-based, *in vitro* mutagenicity alerts by ISS) and systemic toxicity (revised Cramer decision tree), with a supplemental inhalation decision tree, and run using Toxtree software (version 3.1.0). Based on an *in silico* prediction of mutagen, or Cramer class III, II, or I, a threshold of toxicological concern (TTC) value of 12, 90, 540, or 1,800 µg/day was assigned. In parallel, the chemical vapor pressure was generated using the MPBPWIN™ (version 1.43) model available through the US EPA EPI Suite™ program, and used to estimate headspace mass assuming ideal gas behavior and based on a 100 mL headspace volume. From this information, a toxicology-based maximum recommended solution concentration was calculated as the ratio of the TTC to the headspace mass multiplied by 100%. By this framework, the maximum recommended solution concentration was a function of predicted toxicity and chemical volatility. The approach was tested against a published dataset of 144 chemicals with repeat exposure inhalation toxicity data and performed well, with safety margins above 1 for 98.6% of chemicals and above 10 for 95% of chemicals. This framework was used to screen chemicals and either exclude odorants where the recommended concentration was too low to allow reliable perceptual ratings or flag certain chemicals for additional evaluation. Two notable limitations of this approach are the inability to safeguard against irritation and identify asthmagens. However, known asthamtics were excluded from the study and an irritant response would be expected to be transient under the acute exposure study conditions. In summary, an *in silico* framework to derive a toxicology-based maximum recommended solution concentration for chemicals was developed using open-source models and software, and used to support the safety of a psychophysical study of novel odorants.