Rapid Dosimetry in a Tiered Chemical Screening Process for Military Personnel: Toxicokinetic Considerations for a Case Study with *In Vitro* Neurotoxicity

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Abstract:
Background and Purpose: The Air Force Research Laboratory's Predictive Risk Team is developing tools and processes for rapid assessment of human health risks from a variety of threats, including potential exposure to hazardous chemicals. Rapid dosimetry models facilitate interpretation of high throughput in vitro screening data by translating in vitro assay concentrations to external exposures that are expected to cause toxicity in humans. As part of this initiative, the Predictive Risk Team is repurposing an existing US Environmental Protection Agency (EPA) high-throughput toxicokinetic modeling application ("httk") for US Air Force (USAF) population risk assessments. Specific modifications include incorporating the ability to evaluate the impact of demographic differences (e.g., age, gender, ethnicity/race) on absorption, distribution, metabolism, and excretion and thus on human equivalent doses (HED). Furthermore, 5 published sources of clearance (metabolism and excretion) parameter values for httk are available in the literature; HED differences based on clearance source were also evaluated.

Methods: This case study considered substances of interest having known or suspected neurotoxicity, specifically the 220 substances tested in vitro at Sanford Burnham Prebys (SBP) (Bang, 2022). The httk rapid dosimetry model has been applied to HED estimation using five overlapping, but often substantially different, sets of measured/estimated clearance parameters. The US general and USAF populations were simulated using the Monte Carlo simulator from httk. To compare sensitivity of the U.S. national population HEDs to the clearance parameter source, population HEDs (50^{th} and 95^{th} percentile [HED_{50} and HED_{95}]) based on each source were derived. These HED values were derived for the 105 SBP test substances for which all five sources reported a clearance rate, and the ranges of HEDs across sources and substances were determined. To improve the relevance of httk-derived risk evaluations to the USAF, the importance of demographic characteristics was tested by performing a sensitivity analysis in which httk source parameters were restricted to limited ranges/demographic categories (one parameter at a time) for five structurally diverse test substances from the SBP list (permethrin, 2-mercaptobenzothiazole, aldrin, acetopromazine maleate, and cyanamide).

Results: US EPA's httk implementation uses the national population (or segments thereof, e.g., adults only) as characterized in the National Health and Nutrition Examination Survey (NHANES). The USAF population differed from the general population primarily in terms of gender distribution and age, with the USAF having a larger proportion of males vs. females and an age distribution skewed toward younger adults. Comparative simulations of these demographic factors for five test substances found limited impact of gender and ethnicity/race on HED_{95} values. Weight category had a notable impact. For example, the permethrin HED_{95} for obese males was 2.8-fold lower than for underweight males. Likewise, the permethrin HED_{95} was sensitive to age (2.5-fold higher for 18-year-old vs. 66-year-old males), an observation consistent with the relationship between age and bodyweight category. The most notable finding from the model sensitivity analysis was the importance of the intrinsic clearance parameter source and the over-representation of values from a single

source among the highest HEDs. For each of the 105 substances with 5 available published sources for clearance values, the highest and lowest HED_{95} values were identified and their maximum:minimum HED_{95} ratios were computed. When Sipes et al. (2017) values, which were predicted with SimulationsPlus's ADMET Predictor®, were included in HED ratio derivation, the median and 95th percentile HED_{95} ratios were 21.4 and 1468, respectively. If this source was excluded, the median and 95th percentile HED_{95} ratios were almost 3-fold lower (7.73 and 559, respectively).

Conclusions: Httk-derived HEDs for evaluated potential neurotoxicants were sensitive to the ages and bodyweight categories of individuals under consideration, thus assessments based on the national population will differ from assessments based on an age-restricted subpopulation such as the USAF. Further, parameters for kidney function (renal clearance) were restricted to exclude kidney failure based on the assumption that it would exclude personnel from active duty. Overall, these restrictions led to slightly higher HEDs for the USAF compared to the NHANES population, and HEDs for enlisted USAF personnel were slightly higher than officers, primarily due to the difference in median age. Ultimately, the most sensitive parameter was the value for intrinsic clearance (metabolism). Multiple sources in httk are available from which clearance parameters of can be chosen. Risk assessors should consider both the suitability/reliability of the available sources and the purpose of the assessment when selecting among clearance parameter sources for use in an assessment. For assessments with the USAF population, a prioritization scheme was implemented which automatically selects experimental clearance values if available and resorts to predicted values if needed. Sources were also prioritized by robustness of supporting data and biased for conservative HEDs when of similar quality.

References: Bang A. 2022. Enhancement of a predictive toxicology toolbox via multi-parametric data informed QSAR modeling of benchmark toxins. Sanford Burnham Medical Discovery Institute, La Jolla, CA. Mullenger CR, Zehner G. 2020. A statistical matching procedure to increase diversity of the United States Air Force anthropometric database. Wright-Patterson Air Force Base, Ohio USA. AFLCMC/WNU. AD1109537. Sipes et al. 2017. Environ. Sci. Technol. 51:10786.

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