2023 SOT Annual Meeting & ToxExpo
Session: Medical Devices
Poster: P299
Wednesday, March 22, 2023
10:45am - 12:30pm

# Ranking Surrogate Suitability for Read-Across of Medical Device Extractables: A Case Study of Irganox-Related Compounds

**Rachel Y. Chang, Ph.D., DABT; Patricia M. Clyde, Ph.D.; Pranav A. Mashankar, M.S.; Joel M. Cohen, Sc.D., DABT**

Toxicological risk assessment of medical device extractables often deals with data lacking target chemicals, in which a read-across approach may be required to derive tolerable daily intakes (TDIs). In the absence of regulatory recognized standards or guidances, we developed a framework for selecting and evaluating the suitability of potential surrogate compounds for the purposes of toxicological risk assessment conducted in accordance with ISO 10993-17. Suitability of surrogate candidates is evaluated in four weighted domains: chemical structure and reactive functional groups, physicochemical properties, *in silico* toxicity predictions, and metabolic profiles. A cumulative suitability score (SS) is then assigned to surrogates in order to assess their relative suitability for read-across to the target compound. Here, we present a case study evaluating appropriateness of a group of Irganox compounds as surrogates for a common medical device extractable compound, Irganox 259. Irganox 259 is an antioxidant commonly found in medical device extracts that is added to stabilize organic substrates such as plastics, synthetic fibers, and elastomers. In this case study, the target compound is assumed to be extracted from a long-term implant device with direct blood contact, with an exposure period of ≤1 year. Our test set comprised of 16 candidate surrogate chemicals all sharing some aspect of the core (3-(3,5-ditert-butyl-4-hydroxyphenyl)propanoate) substructure with the target compound, while some surrogates also include unique functional groups such asamides, and thioethers. All Irganox compounds evaluated have robust toxicity data packages to facilitate direct comparison of surrogate *vs.* target toxicity across relevant endpoints, and to evaluate the effectiveness of our proposed read-across suitability ranking framework. Irganox compounds are not expected to pose genotoxicity or carcinogenicity risk based on *in silico* predictions and experimental data. Therefore, non-cancer TDIs are derived based on subchronic oral toxicity data in rodents. Consistent with ISO Standard 10993-17 uncertainty factors are applied as follows: 10 for extrapolation from rodents to humans, 10 for interindividual variability, and 10 for route-to-route extrapolation. Relative toxicity between surrogate and target compounds is evaluated by calculating the ratio of TDIs (surrogate TDI / target TDI). For candidate surrogate chemicals with relatively high suitability scores, the TDI ratios ranged from 0.45 to 6.21 with a variance of 5.65 suggesting relatively consistent toxic potency. In contrast, for candidate surrogates with low suitability scores, TDI ratios ranged from 0.18 to 107, with a corresponding variance of 1,368 suggesting a wider distribution of potencies. In an F-test, a statistically significant difference in variances is reported between the high and low suitability groups, $F(7,7) = 0.041$, $p < 0.001$. These findings demonstrate that a read-across framework based on chemical structure, physicochemical properties, *in silico* predictions, and metabolic profiles may be effective in identifying surrogates with similar potency/TDIs (within an order of magnitude) y to the target compound.