2024 SOT Annual Meeting & ToxExpo
Session: Medical Devices
Poster: P483
Monday, March 11, 2024
9:15 AM – 11:15 AM

Derivation of Fit-for-Purpose Non-Cancer Duration-Based TTC Values for Medical Device Constituents

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The threshold of toxicological concern (TTC) is a concept broadly accepted by regulatory bodies in assessing human health risk to chemical exposure. Separate TTC values have been developed to be protective for cancer and non-cancer effects for lifetime exposures. Per ISO/TS 21726, the TTC values (derived from ICH M7(R1)(2017)) for medical devices (MD) are selected based on duration of body contact and are presumed to be protective for both cancer and non-cancer effects that occur following patient exposure to a constituent released from a medical device. Although ISO/TS 21726 allows use of lifetime Cramer Class TTCs to assess non-genotoxic constituents, the lack of duration-based, Less-Than-Lifetime (LTL), non-cancer TTCs remains challenging in assessing MD constituents without toxicity data. Munro *et al.* (1996) and recently US FDA CFSAN (2022) and Patlewicz *et al.* (2022) demonstrate that TTC stratification according to Cramer Classification requires a fit-for-purpose consideration based on the chemical space in which the concept is applied. MD materials comprise a diverse and likely unique chemical space, unlike the original 613 compounds evaluated by Munro *et al.* (1996). This project aims to derive non-cancer, duration-based TTC values that are applicable to assess MD constituents. To develop thresholds applicable to medical devices, chemical libraries of MD extractable compounds were collected from testing laboratories and industry. Available toxicity data was obtained from the European Chemicals Agency (ECHA) database. The ECHA database was selected because it is open access, curated, and data rich. The following criteria were applied using expert judgment from experienced toxicologists for inclusion of that compound in the derivation of a TTC: 1) data had a reliability (Klimisch) score of 1 or 2; 2) the compound was non-genotoxic; 3) the available data were chemical-specific (*i.e.*, no read-across or mixtures); 4) only point of departures (POD, *e.g.*, NOAELs) from oral administration were selected; 5) chemical classification for inorganics, proteins, high MW polymers, APIs, and very potent carcinogens were excluded. To derive LTL non cancer TTCs, the most relevant PoDs from short-term (*i.e.*, ~30 D), subchronic (~90 D), and chronic systemic toxicity studies, as well as reproductive and developmental toxicity studies were evaluated using a cumulative frequency distribution, and nonlinear regression analysis to derive a 5th percentile value for each timepoint. A modifying factor (MF) of 100 (uncertainty factor: 10 each for intraspecies, interspecies adjustment) was applied for TTC derivation. No other UFs were applied. More than 1,000 MD extractable compounds were considered and screened against the criteria for inclusion. The preliminary TTC values range between 160-50 µg/kg/day for short-term to chronic exposure durations. This approach is in line with ISO 10993-1 and the most recent ISO 10993-17 framework for duration-based MD evaluation. The proposed TTCs are intended to be protective for systemic and reproductive/developmental toxicity from extractable compounds from MDs and are higher than the cancer ISO/TS 21726 TTC values and the most conservative current Cramer class III TTC value. Ongoing work aims at increasing the database of MD-specific extractables to further support these non-cancer TTC values. TTC is an indispensable tool for the toxicological risk assessment of medical device extractables lacking toxicity data, and these MD-specific duration-based non-cancer TTC values will allow for a more appropriate evaluation of medical device constituents.

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