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# Applying $EED_{max}$ Approach from ISO 10993-17:2023 to Risk Assessment of DEHP

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Toxicological risk assessments of phthalates are burdened by their complicated toxicological profiles, where critical effects range from systemic toxicity, to carcinogenicity, to reproductive or developmental toxicity. Using a long-term critical effect like cancer as a point of departure (POD), and conservatively assuming that the maximum extracted amount of a phthalate from a medical device represents a patient's daily, lifetime exposure to a compound, may result in an overly conservative margin of safety (MOS). The recently updated International Organization of Standardization (ISO) Standard 10993-17:2023 provides guidance for calculating exposure duration-specific MOSs. Under the guidance, worst-case estimated exposure dose ($EED_{max}$) values are calculated for various endpoints of assumed constituent exposure. Notably, the derivation of $EED_{max}$ values includes a scaling factor (SF), which is the ratio between the maximum quantity of devices expected to be used in a patient at one time and the quantity of devices used in the extraction study. Tolerable intake (IT) values based on critical effects that are appropriate for each duration-based endpoint are used to derive exposure duration-specific MOSs. Here, we present a case study that compared risk assessment under the new ISO Standard to the previous assumed release approach, while characterizing the duration-specific toxicological risk posed by phthalates such as di(2-ethylhexyl) phthalate (DEHP). Once used as a plasticizer in consumer products and medical devices, DEHP is being phased out due to human health concerns. The critical effects of DEHP vary, since DEHP is classified as a Category 1B reproductive toxicant and an endocrine disruptor by the European Commission, and a Group 2B carcinogen by IARC. In this case study, DEHP was quantified at 100 µg/device following the exhaustive extraction of three long-term implant medical devices. One device is intended to be used per patient over > 10 years. Three approaches were used to quantify DEHP's toxicological risk, with the first two using SFs of 1 to derive the $EED_{max}$ values. Estimated exposure doses were either: (1) based on the assumed release approach, where the maximum extracted amount of DEHP equals the patient's daily dose for a lifetime; (2) based on the time period-specific approach, where separate $EED_{max}$ values were calculated for acute, subacute, subchronic, and chronic durations per ISO Standard 10993-17:2023; or (3) identical to the second approach except that its $EED_{max}$ was multiplied by an SF of 3 rather than 1. Carcinogenicity was the most sensitive effect following continuous, long-term DEHP exposure; therefore, the TI for approach (1) was based on the California Office of Environmental Health Hazard Assessment (CalOEHHA) human cancer slope factor of 0.0022 $(mg/kg\text{-}day)^{-1}$. Since the critical effect posed by DEHP was dose- and time-dependent, the subchronic and chronic TIs for approach (2) were based on the human cancer slope factor, while the acute and subacute TIs were based on the reproductive toxicity POD used in CalOEHHA's parenteral maximum allowable dose level (MADL) derivation. Uncertainty factors consistent with ISO Standard 10993-17:2023 were applied to the TIs, as necessary. MOSs for each approach were calculated by dividing the $EED_{max}$ values by their respective TIs. The MOS calculated using approach (1) was 3.2. The MOSs for approach (2) were calculated to be 429, 857, 90, and 1,125 for acute, subacute, subchronic, and chronic exposure, respectively, while the MOSs for approach (3) were 1,200, 3,000, 225, 4,500, respectively. The MOS for approach (1) was 100-fold smaller than the MOSs derived according to ISO Standard 10993-17:2023 for approach (2), indicating the assumption that the patient was repeatedly exposed to the maximum extracted amount of DEHP was an exaggeration of the dose the patient was likely to receive during clinical use of the device. Since the bioavailability of extractables is likely to peak

shortly after the medical device's implantation and decline (or become negligible) over a chronic duration, PODs based on cancer effects may not be appropriate for assessing all endpoints. These findings demonstrate that in the absence of experimentally derived kinetic release data, the $EED_{max}$ approach outlined in ISO 10993-17:2023 provides a useful framework for deriving exposure duration-specific TIs and MOSs. Additionally, the MOSs for approach (3) were approximately threefold higher than those of approach (2). Despite DEHP being quantified in units of µg/device in the extraction study, the number of devices intended to be used at one time (1 device) did not match the number of devices extracted (3 devices). Under ISO Standard 10993-17:2023, an SF of 3 was used to derive the $EED_{max}$ values for approach (3), resulting in artificially inflated MOSs without clear scientific justification. Consideration should, thus, be given to ensure the laboratory matches the manufacturer's definition of "device."