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What is a More Conservative Approach for Risk Assessment? Comparing Materials Characterization Data with an Extractables Profile for a Permanent Orthopedic Implant

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ISO 10993-18, Section 5.2.2, states that "the information obtained can be sufficient to identify all biological hazards arising from the chemical constituents of the material for inclusion in the toxicological risk assessment [TRA]." However, materials characterization data is typically used to inform chemistry profiles and little guidance is provided regarding how to leverage this data for risk assessment. In this case study, a permanent implant orthopedic medical device company compared the results of a TRA conducted with data from analytical methods to a TRA with data generated by gathering information on the contact chemicals in accordance with ISO 10993-18, Section 5. The objective of these risk assessments was to develop an estimate of the toxicological risk to the devices by deriving tolerable intakes (TIs) to each device-derived chemical entity and comparing the overall hazard profiles. Two test articles – plates and screws – were independently extracted under exhaustive conditions in water, hexane, or IPA at 50°C for 72-hour iterations. Extracts were analyzed for volatile, semi-volatile, and non-volatile organic and inorganic compounds. Twenty-two chemical constituents (and 12 elements) were identified in total for plates and screws from the exhaustive extraction study. For the materials characterization approach using information gathering, 41 compounds were identified that could potentially contact the plate, screw, or both devices from the manufacturing, packaging, and sterilization processes. For the contact chemical TRA, we conservatively assumed 0.014 µg/device to be the exposure level for each of the 41 contact chemicals identified in the plate and screw manufacturing and processing steps. We used data from the total organic carbon (TOC) testing that was conducted on a worst-case representative device that went through all manufacturing processes for both the plates and screws. Additionally, since the TOC testing was conducted on a smaller representative device, the assumed exposure level (0.014 µg/device) was adjusted upwards by a scaling factor to account for the total anticipated clinical exposure of the plates and screws. The TRA results indicated that all margins of safety (MOSs) were >10 for the extractables profile, while not all MOSs were >10 for the contact chemical TRA. In conclusion, the contact chemical profile vastly overestimates patient exposure and is the most conservative approach to establish potential toxicological risk.