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Creating Toxicological Risk Assessments for Medical Devices

There has been a substantial increase in the medical device adverse event reports submitted to the Food and Drug Administration (FDA), by 505% from 2012 to 2022. In 2022, nearly 900 medical devices were recalled by FDA, impacting tens of millions of medical devices[1]. Due to unforeseen safety or manufacturing issues, which can cause harm to patients, regulatory authorities are required to conduct medical device safety assessment and recalls in an efficient manner in order to mitigate harm. But how does one take that information and translate it to patient safety? This is where ISO 10993-1 and ISO 10993-17:2023 come into play. In this document we will outline the process by which these standards are used to determine toxicological risk associated with chemicals originating from a medical device.

The importance of a toxicological risk assessment is that it provides an estimate of potential hazards that may be present in a medical device since our ability to predict the final chemistry of the medical device is imperfect, even if it is made using known materials. Various processing steps involved in the manufacture of your medical device may have a significant impact on the chemicals introduced to your patient, including sterilization.

Examples of these impacts include heating processes which increase polymer degradation products, processing steps such as the use of mold release agents, and residues from handling and/or packaging that remain on the final product. It is for this reason that even materials that are not expected to degrade or leachable substances (e.g., many metallic implants) are subject to investigation to ensure that harmful levels of materials have not been inadvertently added to their surfaces.

It is also important to note that any additives or contaminants from the raw material manufacturer, whether or not you have been made aware of them, may also contribute to the toxicological profile of the product.

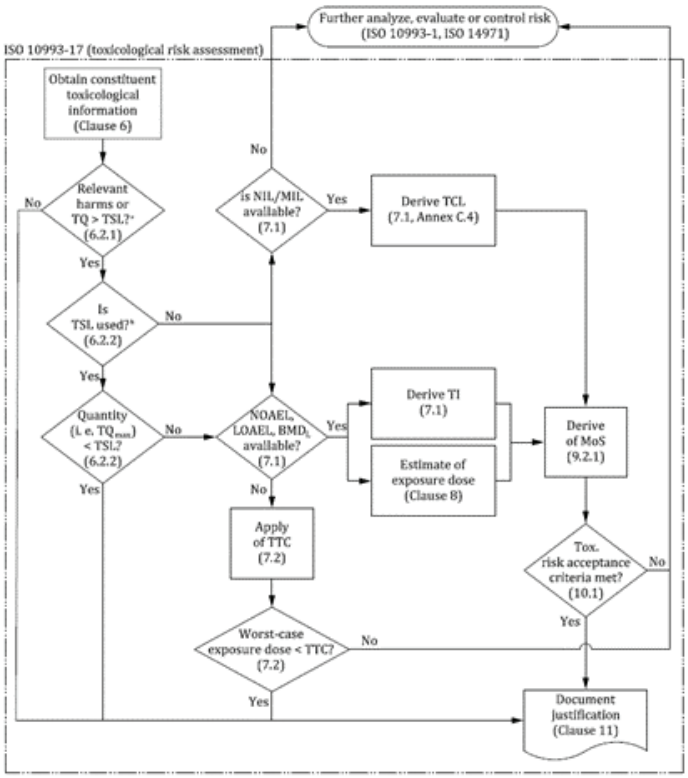
The data that toxicologists use for biocompatibility is often generated from evaluation of the extractables and leachables testing results of a medical devices per ISO 10993-18. This testing will provide information about materials, which have the potential to leach out of your device and into the patient, including their identity and amount. Based on this, the toxicologist can proceed in determining whether the amount of a given material present is toxicologically concerning. Beyond extractables and leachables testing, there may be other device specific considerations, such as the use of degradable materials. In these cases, it is important to understand the chemical breakdown of products and the patient's level of exposure over time to assess potential toxicity.

Note that toxicity cannot be based on material identity alone. The quantity of devices implanted or used by the patient must also be taken into account as material toxicity falls along a spectrum from safe to toxic levels. An example of this is the consumption of water, which is generally considered safe and essential for life; if water is ingested in too high of a quantity, it could potentially result in illness and even death, making an accepted level of a toxin, unacceptable. Thus, one should think of all substances similarly – not as "good" or "bad" but rather as above or below expected toxicity levels. Of course, the key to applying this approach toward medical devices is to determine at what level a substance is considered toxic. Toxicological risk assessment (TRA) is performed in an attempt to identify and estimate the true risks of a medical device, in line with ISO 14971 Medical Devices - Application of risk management to medical devices as described in ISO 10993-17:2023. ISO 10993-17:2023 provides a systematic method for identifying the hazards associated with the medical device, to estimate and evaluate the associated risks, to control these risks, and to monitor the effectiveness of the controls, in order to adequately address these four steps. A general overview of this method is shown in Figure 1.

In order to conduct a toxicological risk assessment of a medical device, toxicologists consult a variety of sources to obtain toxicological data for a given medical device constituent(s) and develops a weight of evidence to characterize the link between the negative effects and the constituent. Examples include:

- U.S. National Institutes of Health's Toxicology Data Network (TOXNET)
- Center for Disease Control and Prevention's Agency for Toxic Substances & Disease Registry (ATSDR)
- European Chemicals Agency's database of Registered Substances (ECHA)

Figure 1 —Critical Toxicological Risk Assessment Activities



- QSAR Toolbox
- Organization of Economic Co-operation and Development's Chemicals Database (OECD)
- ToxPlanet

Other sources used to obtain toxicological data may include various agencies and scientific committees (US FDA, US EPA, NIH, CDC, OSHA, EU-MDR, and SCENIHR) as well as scientific literature (peer-reviewed journal articles).

Toxicological information is available for a large number of substances, but in some cases a substance is identified for which there is limited or no toxicological data available. In such cases, in silico predictive modeling software such as QSAR Toolbox, VEGA QSAR, Toxtree, LeadScope, and DEREK Nexus® can be used to predict toxicity based on the compound's molecular structure.

Using the toxicological data obtained with the help of a variety of sources described above, toxicologists then perform a dose-response assessment to establish the tolerable intake of a given medical device constituent that will not cause any appreciable adverse effect to the patient. This is achieved by using relevant available data from the toxicological literature on the chemical element or compound in question, commonly the no-observed-adverse-effect level (NOAEL) or the lowest- observed-adverse-effect level (LOAEL). These values are then adjusted using a series of uncertainty factors. The uncertainty factors take into account interindividual variability in human populations (e.g., hazards specific to pregnancy that would not apply to those who cannot carry a child), interspecies extrapolation from animal to human, differences in dosing route, and overall data quality, and relevance to patient's exposure to the medical device.

Another factor to consider in the toxicological risk assessment is to measure or estimate the magnitude, frequency, and duration of human exposure to a medical device constituent. One may tolerate a single-time exposure well, but cumulative effects from repeated exposure at that same level may prove to be problematic. Simulated-use extraction or leachable studies, during which data are collected at multiple time-points, can provide (when appropriately justified) release kinetics information for limited, prolonged or long-term contact medical devices. The quantity or total number of constituents (test articles) extracted during chemical characterization is another important factor to consider, as this value is used for calculating the worst-case estimated exposure dose. Perhaps the most important factor in the chemical characterization study of the medical device is the analytical testing parameters and/or methodology used. The medical device testing procedure starts with test article preparation and subsequent testing, which encompass the solvent(s) type and volume, temperature, duration of extraction, number of extraction cycles (if applicable), and reference standard used for quantification all effect the analytical data acquired during chemical characterization studies. The data acquired is compared to Toxicological Screening Limit (TSL), a new concept introduced in the 2023 version of ISO 10993-17. This step is followed by the Tolerable Intake (TI), or Tolerable Contact level (TCL) derivation for materials above the screening limit. TI estimates the daily exposure of an identified constituent that is considered to be without appreciable harm to health, whereas TCL estimates the surface-contact exposure to an identified constituent that is without appreciable irritation.

Once the final TI levels or TCL is determined, it is compared against the amount of constituent that may be released from the medical device (Figure 1). The new ISO 10993-17:2023 also highlights additional consideration for the rate of material release, either based on release data or mathematically adjusted for various exposure durations. Based on this, the substance may be

flagged as being of toxicological concern.Additionally, there may be instances when toxicological concerns remain even after the concerning substance(s) have been reduced to the greatest extent possible. In this case, it may be possible to consider whether the expected benefit of the medical device outweighs the toxicological risk as outlined in ISO 10993-17. Toxicological data for each constituent, justifications and methods used in the derivation and evaluation of a constituent exposure dose for documenting in the report are summarized in ISO 10993-17:2023.

Toxicological risk assessment is an integral part of the overall evaluation of medical devices. There have been great strides made in an effort to reduce the necessity for animal testing on medical devices. The risk benefit assessment of medical devices is a large part of this effort; however, in many cases the need to perform some **in vitro** and **in vivo** biocompatibility studies on medical devices is unavoidable.

Eurofins Medical Device Testing is a global leader for toxicological risk evaluations of medical devices. Our toxicologists are active members of ISO technical committees and provide extensive expertise. With more than 30 years of experience, Eurofins Medical Device Testing will identify and evaluate additives, colorants, processing aids, and any existing toxicity and human exposure risks for your medical device. Our toxicologists will provide you with the technical advice based on decades of industry experience. Our philosophy is to be more than a testing laboratory; we strive to be your global testing partner.

References:

[1] Letter to GAO, re. FDA Oversight of Medical Device Recalls. Pittsburgh Post Gazette. 13 December 2023.

[2] US-FDA Guidance Use of International Standard ISO 10993 -1, "Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing within a Risk Management Process. Guidance for Industry and Food and Drug Administration Staff" of 8 September 2023.

[3] ISO 10993-1:2018, Biological Evaluation of Medical Devices — Part 1: Evaluation and testing within a risk management process.

[4] ISO 10993-17:2023, Biological Evaluation of Medical Devices - Part 17: Toxicological risk assessment of medical device constituents.

[5] ISO 10993-18:2020, Biological Evaluation of Medical Devices - Part 18: Chemical characterization of medical device materials within a risk management process.

[6] ISO 14971:2019, Medical Devices – Application of risk management to medical devices.