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Toxicological Risk Assessment of Medical Devices: An Overview

As Swiss physician, alchemist and astrologer, Paracelsus, stated "All things are poison and nothing is without poison; only the dose makes a thing not a poison." This is now understood to be a basic principal of modern toxicology. The risk management process utilized for biological evaluation of medical devices is predicated on this basic principal and underscores the necessity to establish allowable limits for leachable substances as outlined in ISO 10993-17 - *Establishment of allowable limits for leachable substances.* The FDA requires a thorough toxicological risk assessment to be performed for most medical device submissions. These assessments are founded on the notion that if all of the constituents of a medical device are known, then the safety of the device can be assessed based on the toxicology of those constituents.

Toxicological risk assessments are performed in four primary steps in a scientific 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.* These primary steps are:

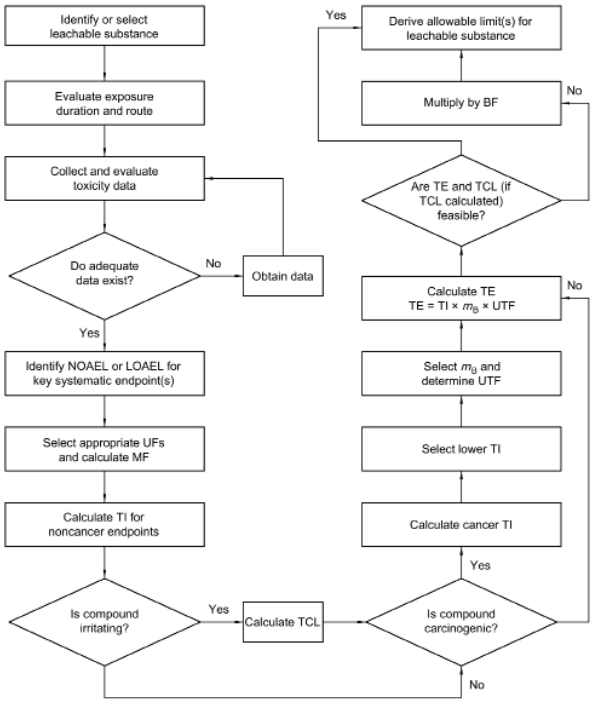
- Hazard Identification
- Hazard Characterization
- Exposure Assessment
- Risk Characterization

ISO 10993-17 does not prescriptively define a procedure to complete these four steps. Instead, ISO 10993-17 provides a systematic method for assessing the wealth of complex toxicological data that varies widely in quantity and quality, in order to adequately address these four steps. A general overview of this method is shown in Figure 1.

The first step is to identify the potential hazards that a given medical device poses to the patient. Identification of these hazards is based on determining the relevant exposure duration and the relevant route of exposure for a given device. It is important to note that in many cases, determining these hazards are not straightforward. One must keep in mind the potential for indirect contact to a patient. For example, an IV bag does not come into contact with a patient, however the solution of pharmaceutical inside the bag will directly contact patient. Thus, IV bags must be evaluated as if they were to contact the patient.

The second step is to characterize any potential hazards with the compounds identified by extractable/ leachable studies. This is done by an extensive scientific evaluation of any

Figure 1



available toxicological data related to each compound. There are a variety of databases that are used to search for toxicological information, including:

- U.S. National Institutes of Health's Toxicology Data Network (TOXNET)
- U.S. Department of Health and Human Services' National Toxicology Report (NTP)
- Center for Disease Control and Prevention's Agency for Toxic Substances & Disease Registry (ATSDR)
- European Chemicals Agency's database of Registered Substances (ECHA)
- Organization of Economic Co-operation and Development's Chemicals Database (OECD)

In the event that there is limited or no toxicological data available for a given leachable, the toxicity of the compound can be predicted using its chemical structure. The software available for these in silico toxicological predictions includes ToxTree and Derek Nexus. Second, it is determined during this characterization whether there is adequate data to perform an appropriate evaluation of the given device.

Third, allowable limits for exposure to the leachable compounds are derived (Figure 1). Typically this will be done by applying an uncertainty factor method to calculate tolerable exposure and intake limits. This is achieved by using relevant available data from the toxicological literature on the leachable compound in question, including the no-observable-adverse-effect level (NOAEL) and the lowest-observable-effect level (LOAEL). These values are then divided by a series of uncertainty factors. These factors take into account interindividual variability in human populations, interspecies extrapolation from the available data, and overall data quality. The ultimate goal of this step is to establish the tolerable exposure of a given leachable that will not cause any appreciable adverse effect to the patient.

The fourth and final step in the toxicological risk assessment of medical devices is the overall risk characterization. During this step, the benefit of the medical device and the risks associated with the device (which were identified and characterized in the previous steps) are weighed and an assessment provided. A feasibility evaluation on the device is performed in order to determine if it is technically or economically feasible to reduce the amount of any compounds that are above the tolerable exposure limits. While toxicological risk assessment of medical devices errs on the safe side when it comes to leachable compounds, if a device contains leachable compounds above the calculated tolerable exposures, the benefit of the device should be considered. In short, the greater the health benefit anticipated from the use of the device, the greater the health risk that can be accepted. In certain circumstances, if those leachable compounds the device contains pose a toxicological concern and have already been reduced to the greatest extent possible, the tolerable exposure limits of a highly beneficial device can be modified by introducing a benefit factor (BF) in order to derive allowable limit. However, meeting these new allowable limits is required.

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 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 to ensure the success of your product development and the necessary regulatory compliance expertise to support your international regulatory submissions. Our philosophy is to be more than a testing laboratory; we strive to be your global testing partner.

References:

Use of International Standard ISO 10993 -1, Biological Evaluation of Medical Devices - Part 1: Evaluation and Testing within a Risk Management Process. N.p.: Food and Drug Administration, Sept. 2020. PDF.

ISO 10993-17: Biological Evaluation of Medical Devices — Part 17: Establishment of Allowable Limits for Leachable Substances. N.p.: International Organization for Standardization, 01 Dec. 2002. PDF.