Toxicological risk assessments

A toxicological risk assessment or TRA is a multi-step process that estimates the risk of adverse health events from exposure to leachable substances from a medical device. It encompasses the scientific review and evaluation of all relevant scientific data on the toxicity of, and the exposure to, a certain compound or mixture (Younes, 2014). Figure 1 outlines the components of a toxicological risk assessment.

Toxicological risk assessment services conducted by Medical Matters (MM) highlight possible adverse risks to patients' health such as skin/eye irritancy, skin sensitization, genotoxicity, etc. by assessing a product and its ingredients against available information on in vitro tests, animal studies and epidemiological data. The aim of a toxicological risk assessment conducted by MM is to ensure final finished devices are biologically safe and to mitigate potential toxicological risks at an early stage in product development. Where information is not available on particular ingredients, MM advises on toxicity testing to determine whether the ingredient poses a significant risk. MM advices advises clients which services are most suitable to meet their particular requirements. Moreover, all assessments and tests are conducted to meet the requirements of regulatory bodies to ensure continuous market access in established and new geographic markets.

TRA:s provide a scientific evaluation of human health risks associated with the intended use of medical devices, as well as an overall characterization of a medical device that may aid decision-makers in determining whether there is a need for remediation. Moreover, it may contribute to process optimization and can play an important role in future product developments where it can contribute to "quality by design" by supporting the choice for a suitable material given the intended use of a medical device. In this context, the identification of an unanticipated contaminant in the course of chemical characterization may lead to identification of its source in the manufacturing process and process optimizations that prevent further contamination of final devices. On the other hand, chemical characterization may detect an unanticipated impurity in a material that is specific to a certain supplier of that material.

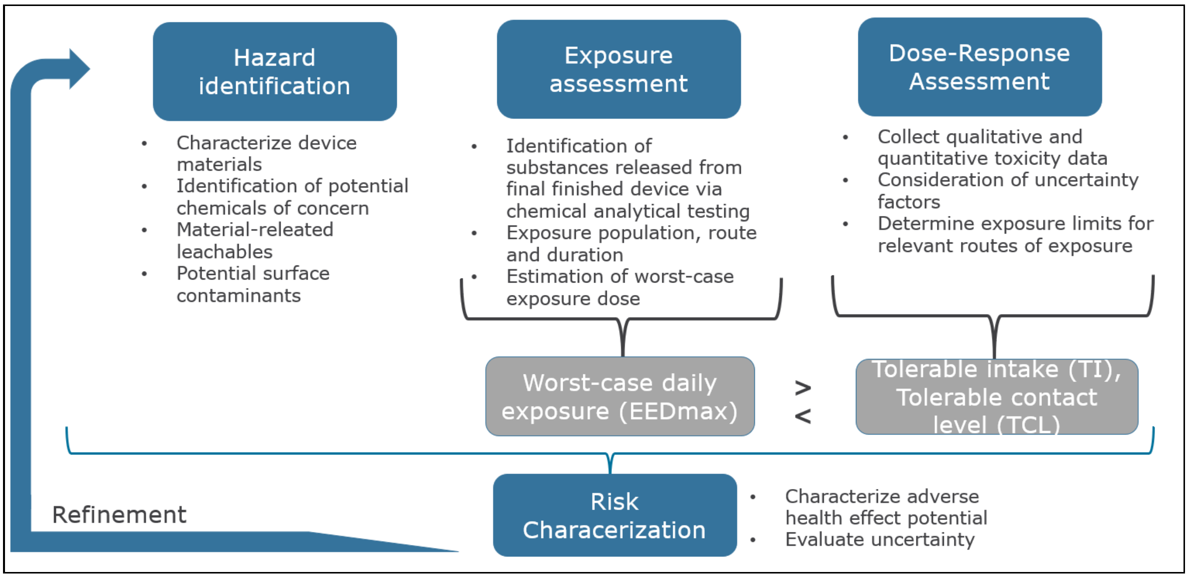

Figure 1: Components of a Toxicological Risk Assessment (TRA)

1 Hazard identification

Hazard identification involves data collection to describe qualitative and quantitative aspects of a medical device. This includes indicated use, material composition, geometry, surface area, manufacturing process, contacting chemicals, cleaning procedure, sterilization procedure, packaging materials, history of clinical use, etc. For new devices, any existing chemical characterization, toxicological and other biological safety data on the predicate device may be considered as far as relevant.

After data collection, the toxicologist identifies the potential biological risks associated with the intended use of subject devices which will be the focus of the risk assessment process. Subsequently, based on the compiled data and identified biological risks, potential gaps in the biocompatibility profile of subject devices are identified and a test strategy to address these gaps is established. For example, limited toxicity data for identified chemicals may prompt further biological testing in order to address specific endpoints, such as genotoxicity. Similarly, a substance of potential toxicological concern might have been identified in the chemical composition of a body-contacting device material and it cannot be ensured that this substance is released below an acceptable level during the application of the device.

Generally, a device is considered biologically safe when it is free from unacceptable biological risks in the context of its intended use. The aim of the TRA is to quantify toxicological risks associated with the use of a medical device. Chemical characterization and TRA are not typically used to address biological risks arising from mechanical failures or improper handling of the device. For example, generation of particles, material breakage, or detachment of coatings are principally assessed within the corporate risk management process. Despite such risk assessments may involve toxicological evaluations, they are not the primary focus of toxicological risk assessments as described in ISO 10993-17. Nevertheless, these risks may become relevant for biocompatibility if clinical data associates such failures with biologically adverse events.

Gaps in a biocompatibility evaluation may be addressed by chemical characterization. In general, chemical characterization along with a toxicological risk assessment shall precede any biological testing for recommended endpoints. This approach is in part to minimize animal testing, as well as to be more efficient in addressing multiple biological endpoints simultaneously. Results from chemical characterization may support that no further biocompatibility testing is needed, or may indicate that further biological testing is needed to evaluate the associated risks with the material formulation and/or extractable/leachable profile of devices. This step-wise process, performing chemical characterization first, then determining which, if any, biological tests are need is part of a risk management approach to reduce unnecessary testing.

1.1 Chemical Characterization

Over the history of the ISO 10993-1 standard, the focus of the document changed from how to determine which biological endpoints have to be addressed by testing (checkbox approach), to an evidence-based scientific approach that considers existing information prior to determining if any testing is needed. Since the 2018 edition of the standard, chemical characterization was made a prerequisite for all medical device types before considering any further biocompatibility testing. Additional testing is usually not necessary, if material characterization (e.g. physical and chemical) demonstrates equivalence to a previously assessed medical device or material with established safety. Moreover, certain biological tests (i.e. those designed to assess systemic effects) are not justifiable where the presence of leachable chemicals has been excluded, or where chemicals have a known and acceptable toxicity profile. If there is limited data on the safety of an identified substance, then the concept of Threshold of Toxicological Concern (TTC) can be used to assess some biocompatibility endpoints (ISO/TS 21726, 2019). Beyond that, the TTC approach may be used to determine if analytical quantification without chemical identification is sufficient to assess the toxicity risk of a device.

In the 2018 update of the ISO 10993-18 guidance chemical characterization is described as a "broad and general process of collecting existing information about a material's chemistry, structure and other properties, and if appropriate, new data, to facilitate the evaluation of these properties." Chemical characterization begins with gathering data from the supplier on the raw materials used within a medical device, focusing initially on qualitative information and proceeding to quantitative assessment if required. This may then be followed with the use of analytical methods to identify and quantify chemical substances released from a medical device that subsequently can be further assessed in a TRA. The purpose of these chemical analyses is to evaluate the risk to a patient from exposure to chemical constituents potentially released from a medical device. For device extractables and leachables that have sufficient toxicological data relevant to the expected exposure (quantity, route and frequency), further testing need not be required. However, especially for devices with a body contact time > 24 h, chemical analysis is usually insufficient to identify all of the risks of the device in its final finished form because it does not consider all relevant aspects of the finished device that could affect the biological response in certain scenarios (e.g., thrombogenicity, implantation). Relevant features beyond the scope of chemical characterization include parameters such as surface properties (e.g., rough versus polished surface) and device geometry.

Chemical analysis is often performed on extracts of a device. A device is incubated in an extraction solvent for a given length of time at a given temperature. The solvent is then analyzed for chemicals that have been extracted. It may be performed with a variety of solvents and with different time/temperature parameters. Simulated use extraction involves using solvents that are most relevant to the clinical application of the device, along with relevant time and temperatures (i.e. 37^{o}C to represent body temperature). Exaggerated extraction involves applying elevated temperature (50^{o}C) and extended time of incubation (72 hours) to increase the amount of extracted chemicals versus the clinical situation. Exhaustive extraction involves performing iterative rounds of extraction on the same test article until the amount of extractable detected is <10% of that measured on the first extraction as a means of evaluating the total amount of each extractable that could potentially leach from a device.

2 Exposure Assessment

An exposure assessment estimates the magnitude, frequency, route, and duration of human exposure to a given chemical. The results of an exposure assessment should take into consideration the worst-case potential amount of chemical exposure and be specific to the route of exposure given the intended use of the device.

3 Dose Response Assessment

A toxicity assessment addresses adverse health effects associated with exposure, including the relationship between magnitude of exposure and adverse health effects. This is frequently a two-step process consisting of (1) hazard identification and (2) dose-response evaluation.

1. Hazard identification is the evaluation of the potential adverse effects to a person from exposure to a given chemical substance. This is determined by reviewing toxicity data for each given chemical. This process primarily consists of finding peer-reviewed chemical-specific toxicity studies via textbooks, online databases, and other toxicological resources. Furthermore, *in silico* tools that use quantitative structure–activity relationship (QSAR) models may be applied and safety data sheets of a material may be reviewed for evidence on the carcinogenicity and other toxicological risks associated with its constituents. The toxicologist evaluates this data to determine if a particular substance is capable of causing specific adverse health effects.
2. The dose-response evaluation quantitatively evaluates the toxicity relationship between dose and incidence of adverse health effects. From these data, the toxicologist derives acceptable exposure levels, which are subsequently used to assess the biological safety of a medical device.

4 Risk Characterisation and Qualification

Risk evaluation combines and summarizes the exposure and toxicity assessments to produce risk estimates and determine the likelihood that adverse health events could occur. To produce a reliable risk assessment, the toxicologist must evaluate the potential for clinical patient exposure to the chemicals identified by laboratory testing. Typically, the toxicologist presents their findings in both quantitative and qualitative statements. The biocompatibility report must disclose all findings and, in particular, must explain the toxicological risk posed by identified chemicals in terms of potential patient exposure.
Risk characterization combines hazard identification and dose-response evaluation to determine the likelihood of specific adverse health events from use of a medical device as intended.
Conservative assumptions/parameters are applied to over-estimate patient exposure. This is achieved, in part, by exaggerated extraction conditions for chemical characterization. In addition, conservative exposure limits are applied with the use of lifetime limits, derived from chronic exposure data whenever available. Similarly, highly sensitive *in vitro* tests, e.g. cytotoxicity tests, may lead to false positive results that overestimate the actual host response under clinical conditions (Gruber & Nickel, 2023; Jablonská et al., 2021; Li et al., 2019; Liu et al., 2018). If the toxicological risk appears unacceptable with these initial conservative assumptions, these may be loosened in a more in-depth refined assessment if justified (see Figure 1). Uncertainty factors may be reduced when chronic exposure data are used to derive acute exposure limits. Moreover, further testing may be conducted to address the risk more precisely.

Contact

MM Toxicology Consulting & Scientific Support
Oberwilerstrasse 78, 4054 Basel, Switzerland;
Email: info@medicalmatters.eu; Homepage: medicalmatters.eu
Telephone: +41 21 515 45 23

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