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Mechanistic Evaluation of Carcinogenicity Endpoint in Chemical Toxicity Risk Assessment for Medical Devices

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Background and Purpose: Evaluation of carcinogenicity risk is required for medical devices intended for long term (>30 day) contact with breached or compromised surface blood path, circulating blood, and tissue/bone/dentin as outlined in Annex A of ISO 10993-1:2018. Assessing this endpoint through risk evaluation of extractables is complex, requiring the resolution of scientific uncertainties, adherence to regulatory guidelines, and consideration of ethical implications. Key challenges include balancing safety with practicality in determining permissible extractable levels and understanding the mechanism of action (MOA) by which a substance induces carcinogenic effects – which is often difficult to establish due to complex interactions, varying doses, exposure routes, and individual patient factors. In this work, we present a framework for navigating these challenges in carcinogenicity risk assessment.

Methods: Previously conducted medical device toxicological risk assessments were surveyed and problem-solving strategies used to overcome commonly encountered challenges in the evaluation of carcinogenicity risk were collated.

In general, mutagenicity and non-genotoxic carcinogenicity endpoints were predicted using a combination of statistics-based (VEGA) and expert decision-based (Toxtree) *in silico* models. Compounds with limited carcinogenicity data are first assessed with an appropriate toxicological threshold concentration (TTC). When application of TTCs does not support a conclusion of tolerable risk, a toxicological risk assessment was conducted with a suitable surrogate.

To avoid overestimation of carcinogenicity risk, exhaustive literature searches were performed, and genotoxicity and carcinogenicity data were evaluated holistically. The following were considered when reviewing relevant toxicity data:

1. Does the MOA support a threshold response?
2. Are the carcinogenicity findings in animal bioassays relevant to patient risk from device use?

Results: For compounds predicted to be nongenotoxic carcinogens, the Cramer Class III-associated TTC of 1.5 µg/kg-bw/day was applied, which has been shown by Boobis *et al*. (2017) and Batke *et al*. (2021) to be sufficiently protective. For compounds predicted to be genotoxic carcinogens, a TTC from ICH M7 and ISO 21726 was applied.

In silico mutagenicity and nongenotoxic carcinogenicity endpoint predictions, combined with the application of the appropriate TTC, can help screen out potentially carcinogenic compounds extracted at low concentrations but are limited in relevant carcinogenicity data, allowing risk assessors to focus on those requiring more thorough review based on carcinogenicity findings.

Linear dose-response approach can be used when mechanistic findings support the existence of a toxicity threshold. Linear no-threshold (LNT) model is used when toxicity threshold response cannot be established at low exposure doses. In general, the LNT extrapolation using a cancer slope to the acceptable risk level of 10^{-5} for medical devices is more conservative compared to an assessment based on a threshold approach.

A few example MOAs that are not relevant to patient risk:

1. PPARα-mediated hepatic tumor in rodent models do not pose a relevant human risk.

When increased tumor incidence is observed only at the primary site of exposure due to inflammatory response from repeated irritation, the carcinogenicity finding may not be relevant to the use of device occurring at much lower concentration *via* different route of exposure.

Conclusions: A through and balanced approach is essential for the evaluation of carcinogenicity endpoints, with careful consideration of MOA and its relevance to patient risk. This helps avoid the overestimation of risk and minimizes unnecessary *in vivo* studies, which can be time-consuming and costly, while ensuring patient safety.