An Evaluation of Risk Assessments on Hexavalent Chromium [Cr(VI)]: The Past, Present, and Future of Mode of Action Research

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Abstract:
Risk assessments for hexavalent chromium (Cr(VI)) have proposed safe drinking water levels protective of cancer ranging from 35 to 100,000 ppt. These values range from below to above the median (1000 ppt) and 95th percentile (3000 ppt) Cr(VI) levels measured in U.S. water sources, and thus have very different implications for human health. Most Cr(VI) risk assessments have relied on the same 2-year cancer bioassay that found that exposures to >=20,000,000 ppt (20 ppm) Cr(VI) cause proximal small intestine tumors in mice and exposure to 180,000,000 ppt (180 ppm) Cr(VI) causes oral mucosa tumors in rats. The differences in safe drinking water levels among the various risk assessments are due, in large part, to mode of action (MOA) determinations influencing the selection of the critical effect for risk assessment, with some risk assessors developing a linear no threshold cancer slope factor based on intestinal tumors and others developing a threshold-based value based on cytotoxicity and regenerative hyperplasia in the proximal small intestine. Important for the field of risk assessment, these disparate approaches have been taken despite considerable mechanistic data characterizing MOA in the target tissues, including several *in vivo* transgenic rodent mutation assays. Herein, we demonstrate that Cr(VI) assessments reveal a high level of variability in review methods, including differential application and subjective scoring of quality and reliability of various *in vivo* studies, criteria applied to consider an *in vivo* genotoxicity study informative when the target carcinogenicity organs are known, criteria applied to consider when target tissue toxicity has been induced in *in vivo* genotoxicity studies, the applicability of genotoxicity results in a relevant tissue but in a species that did not develop tumors, integration of *in vivo* genotoxicity data, interpretation of the likely role of different models of intestinal carcinogenesis, interpretation of evidence of thresholds in Cr(VI) transcriptomic responses, interpretation of pharmacokinetics and PBPK models, and the overall weight of evidence evaluation for intestinal tumors. When topics are placed in the context of regulatory guidance and established methods in MOA analysis, it is apparent that the more recent use of the key characteristics of carcinogens – and evaluation of mechanistic data without important context of dose, temporality, essentiality, biological plausibility, and general pathway considerations standard in MOA analyses – may partially explain the disparate risk assessments for Cr(VI). Collectively, this evaluation demonstrates an apparent shift in the role of MOA in risk assessment decisions, which is likely to influence research programs in the future.