Toxicology-Based Cancer Causation Analysis of CoCr-Containing Hip Implants: A Quantitative Assessment of Genotoxicity and Tumorigenicity Studies

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Abstract:
In this paper, quantitative methods were used to evaluate the weight of evidence regarding a causative relationship between cobalt-chromium (CoCr)-containing hip implants and increased cancer risk. We reviewed approximately 80 published papers and identified no-observed adverse-effect level (NOAEL) and/or lowest-observed-adverse-effect level (LOAEL) values for specific endpoints of interest: genotoxic effects from in vitro studies with human cell lines as well as genotoxicity and tumor formation in animal bioassays. Test articles included Co particles and ions, Cr particles and ions, and CoCr alloy particles as well as CoCr alloy implants. The NOAEL/LOAEL values were compared with body burdens of Co/Cr particles and ions we calculated to exist in systemic tissues of hip implant patients under normal and excessive wear conditions. We found that approximately 40 tumor bioassays have been conducted with CoCr alloy implants or Co/Cr particles and ions at levels hundreds to thousands of times higher than those present in hip implant patients, and none reported a statistically significant increased incidence of systemic tumors. Results from in vitro and in vivo genotoxicity assays, which are relatively less informative owing to false positives and other factors, also indicated that DNA effects would be highly unlikely to occur as a result of wear debris from a CoCr implant. Hence, the toxicological weight of evidence suggests that CoCr-containing hip implants are unlikely to be associated with an increased risk of systemic cancers, which is consistent with published and ongoing cancer epidemiology studies involving patients with CoCr hip implants.

Conflict of Interest
All the authors are employed by Cardno ChemRisk, a consulting firm that provides scientific advice to the government, corporations, law firms and various scientific/professional organizations. Cardno ChemRisk has been engaged by DePuy Orthopaedics, Inc., a manufacturer of prosthetic devices, some of which contain cobalt and chromium, to provide general consulting and expert advice on scientific matters, as well as litigation support. This paper was prepared and written exclusively by the authors, without review, or comment by DePuy employees or counsel. It is likely that this work will be relied upon in medical research, nutrition research and litigation. One of the authors (DJP) has previously testified on behalf of DePuy in hip implant litigation. It is possible that any or all of the authors may be called upon to serve as expert witnesses on behalf of DePuy. Funding for the preparation of this paper was provided by DePuy. The preparation of the paper, including conduct of the literature review, review of the individual papers, integration and synthesis of the findings, the conclusions drawn and recommendations made are the exclusive professional work product of the authors and may not necessarily be those of their employer or the financial sponsor of the review.