

Two Approaches for Assessing Human Safety of Disperse Blue 1

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Disperse Blue 1 is an anthraquinone dye used at low levels in semipermanent hair color formulations. Dietary administration of Disperse Blue 1 in a National Toxicology Program (NTP) carcinogenesis bioassay produced transitional- and squamous-cell tumors, leiomyomas, and leiomyosarcomas of the urinary bladders of male and female F344/N rats. The occurrence of tumors in the urinary bladder of rats was associated with urothelial hyperplasia and the presence of urinary calculi. Despite the occurrence of urinary bladder calculi and other nonneoplastic changes, there was no evidence of urinary bladder carcinogenesis in B6C3F₁ mice fed Disperse Blue 1 in the diet for up to 2 years. A study conducted in rats of the same strain by Burnett and Squire confirmed the occurrence of calculi and transitional-cell neoplasms in the rat bladder. However, no mesenchymal-cell tumors were detected at a comparable dietary level. Further, Burnett and Squire found evidence of reversibility of the proliferative changes in the rat urinary bladder following cessation of treatment at 6 months. Disperse Blue 1 has been tested in a variety of *in vivo* and *in vitro* genotoxicity assays and was negative *in vivo* but produced a weak and mixed pattern of genotoxic responses *in vitro* which may be attributable to a constituent of the commercial preparations. Evaluation of the available data for Disperse Blue 1 and comparison with the responses observed in the urinary bladders of rats administered other rodent bladder carcinogens considered to act through a secondary mechanism indicate that a threshold approach is appropriate for assessing risk. With this approach, an uncertainty factor of 1000 applied to the no-observed-adverse-effect level in the NTP bioassay yielded a safe exposure level of 45-56 $\mu\text{g}/\text{kg}/\text{day}$. In contrast, with a conventional quantitative risk assessment approach, the exposure level corresponding to an upper limit on lifetime risk of 10^{-6} to 10^{-5} was 0.39 to 3.9 $\mu\text{g}/\text{kg}/\text{day}$, respectively. The safe level of Disperse Blue 1 derived using the threshold approach is approximately 20 times greater than the maximum average daily applied dose of 2.7 $\mu\text{g}/\text{kg}/\text{day}$ associated with its use in semipermanent hair color formulations, while the exposure associated with the 10^{-5} risk level using the linearized multistage model in the conventional approach was determined to be 1.5 times greater. Because oral absorption is substantially more than dermal absorption, the actual margin of safety is most likely much greater than either of these comparisons suggests. The difference in the estimates derived using the two approaches demonstrates the importance of incorporating information on the mechanism of action into the risk assessment process.