

**PATHOLOGY REEVALUATION OF THE KOCIBA ET AL. (1978) BIOASSAY OF 2,3,7,8-TCDD: IMPLICATIONS FOR RISK ASSESSMENT**

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*The chronic bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD) reported in 1978 by Kociba et al. has been considered to be the primary evidence supporting its carcinogenicity, and is the basis for most dioxin regulations in North America and Western Europe. Because the histopathological criteria for proliferative lesions in the rat liver have changed significantly since 1978, a reevaluation of the liver slides was conducted recently by an independent panel of pathologists. Using current National Toxicology Program criteria, their study showed, in contrast to the original findings, that about two-thirds fewer tumors were present in the livers of female Sprague-Dawley rats. The no-observed-adverse-effect level (NOAEL) for hepatocellular carcinomas was 0.01 µg/kg/d rather than 0.001 µg/kg/d, which had been reported in 1978. In light of these significant findings, a quantitative dose-response assessment of 2,3,7,8-TCDD was undertaken to predict the potential carcinogenic risks to humans. Risk-specific doses (RsDs) and cancer potency factors (CPFs) were calculated by applying the linearized multistage (LMS) model to the combined incidences of hepatocellular carcinomas and adenomas, classified in accordance with the 1990 histopathological criteria. Based on the weight of evidence regarding the mechanism of action of 2,3,7,8-TCDD, body weight rather than surface area was selected as the appropriate means for scaling rodent data to predict the human response. Using the survival-adjusted data, the RsD for a 1 in 1,000,000 ( $10^{-6}$ ) plausible upper bound (95%) lifetime incremental cancer risk was 370 fg/kg/d based only on the incidence of hepatocellular carcinomas, and 100 fg/kg/d when hepatocellular carcinomas and adenomas were combined. The corresponding upper-bound (95%) CPFs were 2700 and 9700 (mg/kg/d)<sup>-1</sup>, respectively. These results indicate that the carcinogenic risk to humans from exposure to 2,3,7,8-TCDD is at least 16-fold lower than previous estimates derived from the Kociba et al. (1978) bioassay.*