RISK ASSESSMENT OF 2,3,7,8-TCDD USING A BIOLOGICALLY BASED CANCER MODEL: A REEVALUATION OF THE KOCIBA ET AL. BIOASSAY USING 1978 AND 1990 HISTOPATHOLOGY CRITERIA

Dennis J. Paustenbach

ChemRisk—A Division of McLaren/Hart, Alameda, California

Maxwell W. Layard

Layard Associates, 2242 San Antonio Avenue, Alameda, California

Richard J. Wenning, Russell E. Keenan

ChemRisk—A Division of McLaren/Hart, Portland, Maine

The Moolgavkar-Venzon-Knudson (M-V-K) two-stage model for carcinogenesis was used to estimate the risk-specific dose (RsD) based on the incidence of tumors reported by Kociba et al. (1978) for Sprague-Dawley rats exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin (2,3,7,8-TCDD; dioxin). The results from the recently completed (1990) reevaluation of the Kociba et al. study, which used the current National Toxicology Program (NTP) pathology criteria, were also evaluated. Time-to-tumor information for each rat was incorporated into the analysis. Model parameters for the approximate form of the hazard function of the two-stage M-V-K model were determined by maximum likelihood estimation. This simplification was significant but necessary, because laboratory data on the intermediate cell growth rate and the transition rates have not been determined. Estimates of the RsD (10^{-6} risk) (based on the original 1978 histopathology results) were 10 fg/kg/d when carcinomas and hyperplastic nodules were combined and 150 fg/kg/d when only carcinomas were considered. In contrast, using the 1990 histopathology data, the RsD (10^{-6} risk) was 80 fg/kg/d when adenomas and carcinomas were combined and 25,000 fg/kg/d when only hepatocellular carcinomas were considered. Since the two-stage M-V-K model is intended to predict the occurrence of malignant tumors, the mathematically appropriate RsD is 25,000 fg/kg/d (10^{-6} risk). Because the model does not account for pharmacokinetics or the possibility of other toxic effects, the appropriate RsD (10^{-6} risk) for humans should be much smaller. Using the carcinoma data only, a sensitivity analysis of key parameters in the model was conducted. Results indicated that the ranges of plausible values for the RsD (10^{-6} risk) for the original 1978 and the 1990 reevaluation data were 70–2600 fg/kg/d and 120–50,000 fg/kg/d, respectively. The lowest plausible RsD is, therefore, approximately 10-fold greater than the current U.S. EPA RsD (10^{-6} risk) of 6.4 fg/kg/d [which is based on the linearized multistage (LMS) model]. Even though these results

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